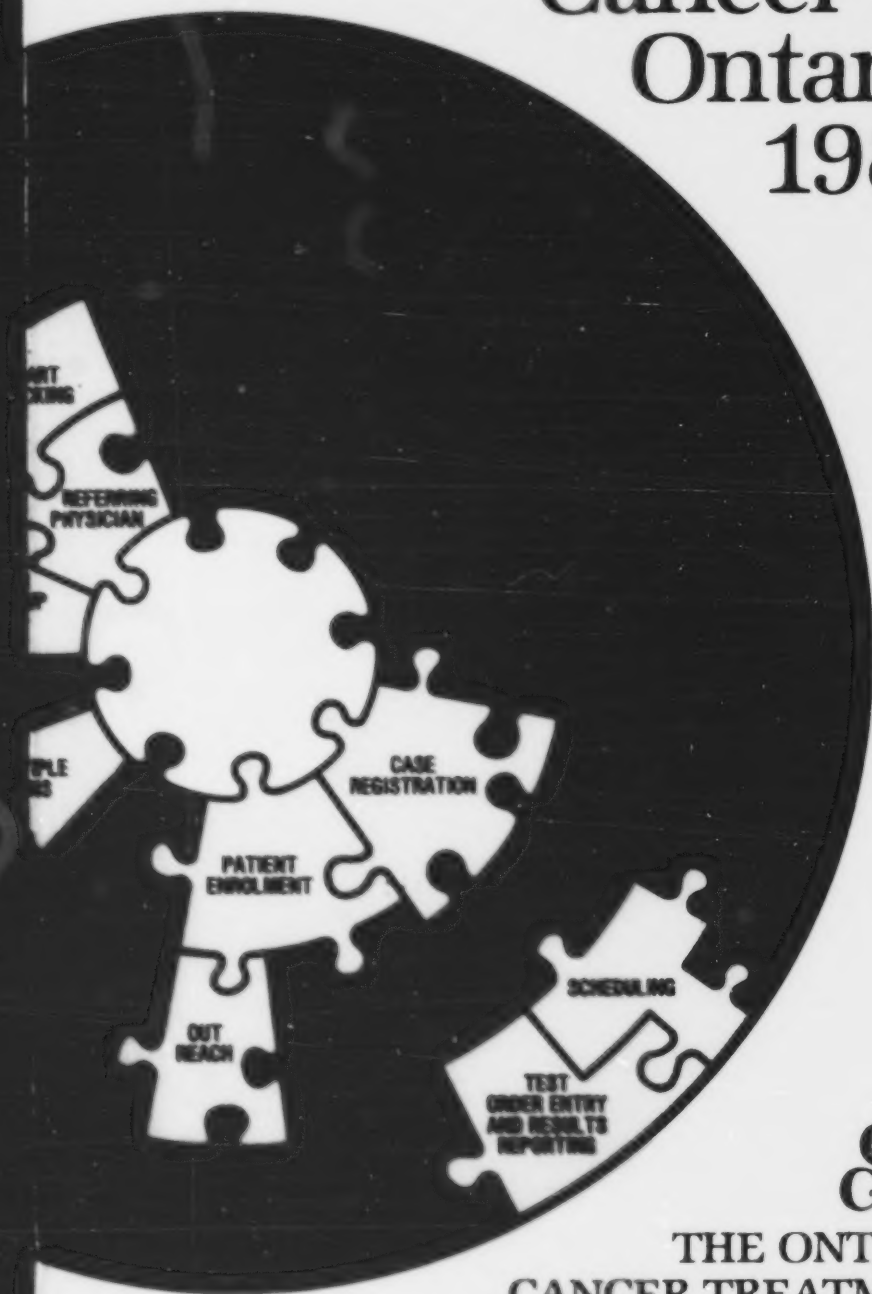
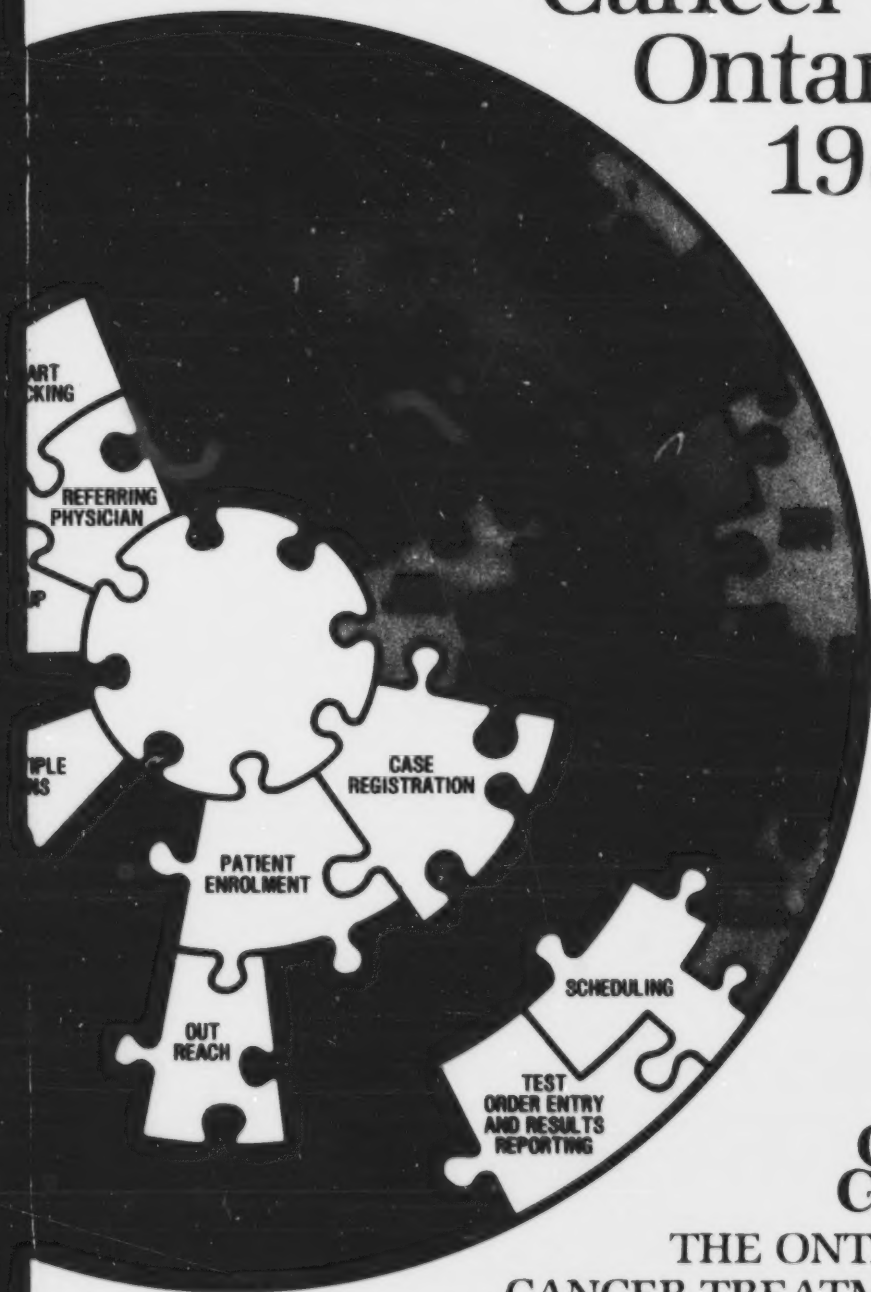


Cancer in Ontario 1984



THE ONTARIO
CANCER TREATMENT
AND RESEARCH FOUNDATION

Cancer in Ontario 1984



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CANCER TREATMENT
AND RESEARCH FOUNDATION

The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

- (a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;
- (b) the transportation of patients and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;
- (c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;
- (d) the laboratory and clinical investigation of cancer problems;
- (e) the co-ordination of facilities for treatment;
- (f) the adequate reporting of cases and the recording and compilation of data;
- (g) the education of the public in the importance of early recognition and treatment;
- (h) the providing of facilities for undergraduate and postgraduate study;
- (i) the training of technical personnel; and
- (j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

CANCER IN ONTARIO

1984

THE COVER

The cover depicts the interlocking character of all of the current computer applications or those planned as future projects. The color keys refer to the five principal information systems — Ontario Cancer Registry and data collection, administration, patient care management, research and statistics — and to potential future applications. In all, this "jigsaw puzzle" illustrates the complexity of modern data handling and the interdependence of administration, treatment management, record keeping and research.

The Ontario Cancer Treatment and Research Foundation
7 Overlea Boulevard
Toronto, Ontario, Canada
M4H 1A8



CONTENTS

Message from the Chairman	1
Executive Director Reports	3

PROGRESS IN CANCER

T-Cell-Antigen Receptor and Its Clinical Implications T. W. Mak	9
Investigating the Effects of Mind on Cancer A. J. Cunningham	13

EDUCATION

Summary of OCTRF Education Activities	21
Relationship between Diet and Colon Cancer: Laboratory and Clinical Studies W. R. Cosbie Lecture 1984 W. R. Bruce	25
23rd Clinical Conference The Treatment of Localized Hodgkin's Disease and Non-Hodgkin's Lymphoma	29
Early-Stage Hodgkin's Disease: A Review of Current Treatment Approaches J. J. Rusthoven	30
The Current Management of Localized Non-Hodgkin's Lymphomas R. G. MacKenzie	38

REGIONAL CANCER CENTRES

Ontario Cancer Foundation

Hamilton Centre	51
Kingston Centre	53
London Centre	55
Ottawa Centre	58
Thunder Bay Centre	61
Toronto-Bayview Centre	63
Windsor Centre	65
Service Load	67
Ontario Cancer Institute Incorporating Princess Margaret Hospital	75
Consultative and Follow-up Clinics by Zones of Service	82
Clinical Consultants at OCF Regional Cancer Centres and the Princess Margaret Hospital	84

SPECIAL SERVICES

Provision of Special Drugs to Treat Malignant Disease	91
Carcinoembryonic Antigen (CEA) and Steroid-Receptor Assays	93
Diagnostic Biopsy Service and Voluntary Reporting by Pathologists	95
Lodges for Ambulatory Cancer Patients	96
Transportation of Cancer Patients	97

RESEARCH PROGRAMS

Summary of OCTRF Research	101
Ontario Cancer Foundation Research Associates in the Health Sciences Complex	105
Reports on Research Projects Supported by the Foundation by City, Institution, Title and Author	106

EPIDEMIOLOGY AND STATISTICS

Cancer Incidence, Mortality and Treatment in Ontario E. A. Clarke, N. Kreiger, L. D. Marrette and C. L. Soskolne	157
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INFORMATION SYSTEMS

Overview of Information Systems J. I. Murphy, W. B. Matte and T. Broz	189
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DIRECTORY

Members of the Ontario Cancer Treatment and Research Foundation and its Committees	207
Foundation Head Office Staff	212

APPENDICES

Appendix A: Bequests and Donations	215
Appendix B: List of Articles Published in 1983 by Research Associates and Grantees, and Members of the Staffs of the Ontario Cancer Treatment and Research Foundation and the Regional Treat- ment Centres	219



MESSAGE FROM THE CHAIRMAN



Photo: Tony V. Hauser

One of the principal accomplishments of the Foundation in 1984 was the development of the Ontario Cancer Registry to the point where it can now provide information on the frequency of cancer for the period 1964-1982; these revealed an increase in cancer cases in Ontario from 17,351 to 31,588 per year during this time. Put more directly, between 1 in 3 and 1 in 4 people can expect to develop cancer during a 75-year lifespan. This trend, which will be accentuated with the increasing age of our population, is reflected in the increasing numbers of patients referred to the Foundation's seven regional cancer centres for consultation, treatment and follow-up.

The Provincial Role Study, for which data collection and fieldwork has now been completed, will provide guidance to the Board and staff of the Foundation to improve the management of cancer patients throughout the Province. All are looking forward to the substance of this report to be received from the consultants early in 1985.

I record with pleasure the reappointment of the Hon. Richard A. Bell, P.C., Q.C., to the Board of the Foundation and express my gratitude to Dr. Douglas Bocking on his retirement after serving as a member for two terms with distinction.

On behalf of the Board, I wish to record with appreciation the continuing support and dedication of the staff of the Foundation.

Finally I wish to thank the Government of Ontario, the Canadian Cancer Society Ontario Division, the many patients, their families and their friends for the continued financial assistance we receive and without which our task would be impossible.

**Michael Meighen, Q.C.,
Chairman**



THE EXECUTIVE DIRECTOR REPORTS

In 1984, an intensive review was made of the programs of the Foundation and our sister organization, the Ontario Cancer Institute, as part of a Provincial Role Study of our two organizations. Input was received from constituencies within the Foundation and the Institute, and in the health science complexes, medical, paramedical, and other bodies throughout the province. We expect that this study, which has stimulated us to consider seriously our present and future activities, will be available early in 1985, as a basis for decision making over the next decade.

The number of patients referred to the Foundation's Regional Cancer Centres continues to increase overall; from 1982 to 1983 the number has increased by 8.9% and these increases place significant strains on our space, equipment and staff. We have attempted to ameliorate these strains by reducing the number of follow-up visits, and by encouraging the centres to develop outreach programs. These create a working relationship between a community-based clinician, who assumes some of the workload in his/her area and the staff member at the regional centre. Also we have moved to shorten the time needed to treat patients with radiotherapy by installing new high-energy linear accelerators in the Toronto-Bayview, London and Hamilton Centres. Furthermore we have undertaken to provide "bridge" financing for a linear accelerator in Thunder Bay and Windsor Centres in the near future. With the support of the Ministry of Health we now pay the transportation costs of children who are referred to any of the pediatric centres in the health science complexes of the province.

The most significant service event in 1984 was the completion of the Role Study and Master Program for the planning of a new cancer centre in Sudbury. We are indebted to the Ontario Cancer Institute for maintaining consultative clinics in Northeastern Ontario and for managing the initial stages of cancer chemotherapy service, which is operated at the Laurentian Hospital in Sudbury under the direction of Dr. Robert Coringham.

Under our research program, a total of eight career scientists have been appointed to the London, Hamilton, Ottawa and Kingston Centres. We have also appointed one new research scholar in London. During the year, the Ontario Clinical Oncology Program began to promote clinical trials of cancer treatment with the support of lottery funds from the Province of Ontario. We have begun preliminary conversations with industry representatives with a view to assessing the effect of hyperthermia in conjunction with radiotherapy and chemotherapy. The Foundation has assisted in the development of a research program into the cause and management of the AIDS syndrome. We have also established contacts with the newly developed Health Research and Development Council of Ontario.

In the field of education we continue to provide undergraduates in medicine with opportunities for exposure to oncologic practice in the various regional cancer centres. Also, for undergraduates in physics, we have instituted a summer studentship program to acquaint them with opportunities for careers in medical physics. With respect to our mandate for public education, which generally is assumed by the Canadian Cancer Society Ontario Division, we have developed in co-operation with the Society, a Cancer Information System. Centred in the Hamilton Regional Cancer Centre, this system will provide telephone access to the public, the media and the profession regarding any aspect of cancer and its control. We are delighted to report that, during the year, we concluded an agreement concerning academic interaction between McMaster University and the Thunder Bay Regional Cancer Centre. Also we have begun planning with other agencies for a program that will reduce cigarette smoking by young people; we hope to continue these activities during 1985 and beyond.

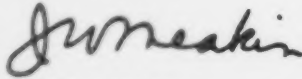
With respect to provincial programs, we are pleased to report that provisional incidence data for cancer in Ontario is now available for the years 1964 through 1982. In the next year, we hope that cancer incidence data will be available within one year of currency. The computerized automation of our regional cancer centres has continued during the year and we hope that this will be completed during 1985.

With respect to the future, we look forward with great interest to the report of the Provincial Role Study, referred to earlier. The Foundation needs to examine its contribution to new areas of need such as palliative care, and the provision of adequate dental care and prosthetics. Also we need to plan for the relocation of the London Regional Cancer Centre, a significant upgrading of the Hamilton Centre, and the start of construction of the new centre in Sudbury. Finally, the steady increase in patients referred to our centres in Toronto and Ottawa will require a significant upgrading of these facilities as well.

As I have said before, the strength of any organization is its people. In this connection I wish to record my gratitude to the many members of the Board and the staff of the Foundation for their continued support. Particularly I would like to note the reappointment of the Hon. Richard Bell to the Board for a second three-year term; to thank Dr. Douglas Bocking, who retired during the year as a Board member, and to report that Dr. George Mok has assumed the responsibilities of Acting Director of the Windsor Regional Cancer Centre. Finally, on behalf of the Foundation, I would like to thank Dr. John Maus for the many years of leadership, which he provided in Windsor.

In closing, I would emphasize that our programs would not be possible without the funding support of the Government of Ontario through the Ministry of Health. We are greatly assisted by the financial support of the Canadian Cancer Society Ontario Division in the construction of new centres and lodges, particularly the new lodge in Hamilton which should be completed during 1985. Also the Division has given support to special programs, such as the Cancer Registry, on a time-limited basis. Finally, I would like to thank the public, principally patients and their families,

who spontaneously have made donations to the Foundation which have become an essential part of our financial base.



J. William Meakin, M.D., C.M., M.A., F.R.C.P.(C)
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the head office of the Foundation.



PROGRESS IN CANCER



T-CELL-ANTIGEN RECEPTOR AND ITS CLINICAL IMPLICATIONS

T. W. MAK, Ph.D.*, *Toronto, Ontario*



The antigen receptor on T-lymphocytes (TcR) is essential for their role in immunity. The receptor is the mechanism that allows T-cells to distinguish between native and foreign substances, preserving the former and eliminating the latter. Normally functioning T-lymphocytes provide powerful protection against certain viral infections. When the system becomes diseased, self-antigens in normal cells may be attacked, causing the destruction that characterizes autoimmune diseases such as rheumatoid arthritis and lupus erythematosus. The destructive power of T-cells is also a major

obstacle to the replacement of diseased or injured tissue by transplantation. Knowledge of the mechanisms underlying T-cell-mediated recognition will expand rapidly as a result of the cloning of the gene encoding for the T-cell receptor. The discovery is too recent to make confident predictions of its practical outcome; however it seems certain that diagnosis will be improved, and possible that new therapies will be developed.

T-lymphocytes have special roles in cancer. Normally, they may recognize some tumors as foreign and destroy them before they have a chance to grow to a dangerous size. When malignant transformation occurs in T-cells, the resulting lymphomas or leukemias are almost always aggressive and resistant to treatment. Evidence is already available that genetic changes in the T-cell receptor occur in T-cell malignancies. Detection of these will improve the classification of tumors, and may provide new approaches to management, based on manipulating the biological properties of malignant stem cells.

Unfortunately, however, while the genetic and molecular mechanism responsible for antibody diversity have been largely elucidated over the last decade, the characterization of the T-cell antigen recognition structure, the T-cell receptor and

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the diversification of the receptor repertoire have been an elusive goal of molecular immunologists for many years. One of the most interesting characteristics of T-lymphocyte behavior is its antigen recognition in the context of the major histocompatibility complex (MHC), a phenomenon known as MHC restriction. Several excellent reviews have been written on this subject recently. This characteristic nature of antigen recognition by T-cells and the repeated failures to isolate the T-cell receptor genes, despite extensive efforts, have led to much speculation as to the nature of these genes.

Based on the rationale that T-cells contain a separate mechanism for antigen recognition, we have cloned and sequenced a human T-cell-specific "message" that specifies part of the T-cell receptor. Subsequent work has demonstrated that the genes of the human T-cell receptor are distinct from the light and heavy chains of immunoglobulin. Their general organization and the mechanisms of generation of diversity are, however, similar to those used by immunoglobulins. Thus T-cell receptor genes appear to be members of the immunoglobulin super-gene family, having diverged before species diverged. Studies using leukemic patients' DNA indicate that the T-cell antigen receptor can be used to identify malignancies of the T-cell lineage.

The availability of the molecular probes for the gene and the knowledge of the primary sequence of the T-cell receptor offer opportunities to investigate clinical situations which involve T-cells. These include T-cell neoplasias, certain autoimmune disease and immunodeficiencies. Several experimental approaches are now possible. With the use of the now-available protein sequence, antibodies can be generated to various parts of the T-cell receptor using artificial synthetic peptides as antigens. These can be used to investigate many possible abnormalities involving T-cell receptor. For example, it is possible that, under some situations, there may be an increase in the sensitivity of the receptor while in others the receptor density may be low or absent. The former cases may involve certain autoimmune diseases while the latter situations may be found in some immunodeficiencies. The "dissection" of the nature of the T-cell receptor in the three classes of T-cell may further reveal certain features unique to each class. These results may be useful as additional tools to investigate the different clinical abnormalities involving the gene. Yet another approach to a study of defects of T-cells is to examine the "clonality" of T-cell subpopulations by investigating the proportion of T-cell receptors with unique specificities. These situations may be associated with certain immunodeficiencies or neoplasias.

The direct use of the T-cell receptor gene to examine certain clinical situations involving T-cell abnormalities may also prove fruitful. These investigations have already begun. With the use of β -chain cDNA of the T-cell receptor, Drs. M. Minden and E. Gelfand in collaboration with us have shown that in 12 patients with T-cell leukemias, the genes are rearranged when compared to their germ line DNA. Furthermore, these molecular probes have been used to study patients in remission and relapse. As well, the study of bone-marrow transplants should be fruitful. Taking

advantage of the finding that the receptor "message" is elevated in thymic leukemia, in situ hybridization has also been used to detect neoplastic T-cells on a single cell basis. This assay has certain advantages in the study of lymphoma sections and can be used on frozen cell samples.



INVESTIGATING THE EFFECTS OF MIND ON CANCER

A. J. CUNNINGHAM, Ph.D.* *Toronto, Ontario*



Mental and behavioural events have become major contributors to disease in Western countries: Examples are the effects of smoking and overconsumption of food and alcohol, the pervasiveness of mental disorders, and effects of "stress" as seen in the association between type A personality and coronary heart disease. For cancer, the second most important cause of death in Western countries, an intriguing situation exists. It was widely believed for many centuries that emotional states, particularly depression, could favour the development of the disease¹.

This idea fell into disrepute with the great technical advances of medicine in the twentieth century. Yet there has always been an "underground", claiming that mental factors promote cancer and that psychologically-based therapies could be curative. In the last 10 years or so, psychological approaches, mainly techniques for deliberately visualizing the shrinking of tumors under attack by host defense mechanisms, have become so well known that patients often request them although there are no controlled studies which provide evidence for (or against) the effectiveness of these procedures. Physicians tend to dismiss such psychological therapies, unaware of accumulating evidence that events in the mind may indeed affect the onset, course and outcome of cancer^{2,3,4}. At this stage, there is an urgent need for the systematic investigation of psychological techniques as a possible adjunct to regular medical treatment.

Evidence that Mind Affects Cancer

The strength of the argument for a mind-cancer link lies not in any one experiment or even any one field of research, but in the convergence of evidence from three quite separate areas: Animal experiments, human personality studies, and clinical trials.

Animal experiments. There is general agreement among those studying the psychophysiology of cancer in animals that various stressors, such as shock, handling,

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fatigue, isolation, fear and early life events, can influence tumor growth⁵. Results have been highly variable, however: tumors are sometimes enhanced, and, under some conditions, are inhibited. Sklar and Anisman, who attempted to impose some order on the chaos in this field with their own research⁶ and critical review⁷, concluded that acute stress tended to favour cancer growth, while chronic stress allowed hormonal and immune adaptation and often decreased tumor development. However, if acute stress could be controlled, as in experiments using tumor-bearing rats given an electric shock which they could turn off, tumor growth was decreased. This interesting result was confirmed by another group⁸.

The immune system is usually considered to provide an important natural defense against cancer, and it is of considerable interest that stress affects immune function. Much excitement has been generated by reports from several laboratories that immune depression can be psychologically conditioned⁹. Thus a pathway for possible effects of mind on cancer is beginning to emerge: Mental attitude or expectancy → hormonal response → immune depression → tumor growth.

Human personality studies. A large literature going back more than 30 years describes "retrospective" work, in which personality characteristics of people with cancer have been compared with matched controls who did not have the disease. This work has been criticized, particularly on the grounds that having the disease may alter personality, or at least, alter one's response to questionnaires. However, a small number of "prospective" studies, most of them recent, have included tests of psychological status done before disease onset. Such work suggests that the following factors predispose people to cancer: Lack of closeness to parents, depression, repressive tendencies and non-assertiveness. Another common theme emerging from retrospective studies is inhibition of emotional expression. Also common, although by no means consistent has been the observation that cancer patients have suffered the loss of an important relationship in the years just before diagnosis. Overall, while results vary greatly from one report to another, and negative reports abound, it seems likely that there is an association between personality and risk of cancer, but that this relationship is so complex and variable that it is unlikely to be clearly delineated by such correlative studies.

Effects of psychotherapy. Apart from a number of anecdotal accounts involving small numbers of patients, and informal claims in the popular press, four groups of published clinical trials have described a deliberate attempt to prolong life with psychotherapy. The Simonton group pioneered the use of meditation and visualization against cancer in USA¹⁰; they claim an average survival time among their patients approximately two-fold longer than the U.S. median. Newton¹¹ puts more emphasis on hypnosis in his program, which is run by a group of clinical psychologists conducting individual therapy. Of 105 of his patients who received 10 or more sessions, 57% were alive at the time of his report, while only 18% of those who had only 3-9 sessions still survived. Meares¹² used intensive daily meditation with 73 patients and reported complete remission in five, and partial in five more "in the absence of any organic treatment which could possibly account for it". Most of his

patients had advanced disease. In all of these trials, one might raise the important objection that the patients offering themselves for therapy were a highly select group who may have done much better than average without the treatment. Controlled experiments are needed to overcome this difficulty.

Recently, Grossarth-Maticek and colleagues¹³ reviewed what appear to be the only published controlled trials of the life-enhancing effects of a form of psychotherapy for cancer. Over a number of years, this group tested a particular type of therapy, called "creative novation", which attempted to help patients solve problems in their lives by closely examining and changing their beliefs and expectations about them. Relaxation and suggestion were used in addition to counselling. Two experiments with breast-cancer patients compared this therapy with more traditional behaviour modification, psychoanalytic therapy, or none. All therapy consisted of 30 individual sessions. Creative novation increased average life span by about six months. Behaviour modification, or sessions with relatively less experienced creative novation therapists had less, but still positive effects, while the analytic psychotherapy had no effect or shortened patients' lives.

Why have Physicians and Biologists Largely Ignored a Possible Influence of Mind?

There seem to be four main reasons. First, many have held a faulty concept of the way cancer (and many chronic diseases) develop. The common assumption is that there is a single, usually external cause, and that the only way to treat is to destroy all cancer cells. This view is based on a nineteenth century model of infectious disease: It ignores the evidence that clinical cancer is not a simple "accident" but represents the failure of a variety of natural regulating mechanisms, e.g., enzymes within cells, local and circulating hormones, and the immune system. These controls can be influenced by the body's highest "level" of control, the brain/mind. Secondly, much of the psychological evidence is recent and has been published in non-medical journals. Thirdly, as we have seen, the case for mind influencing cancer rests on the weight of diverse evidence rather than on any single highly visible and unambiguous trial. Finally, there is a lack of understanding of the profound effects which symbols, i.e., words, ideas, information, can have on the body: as many workers have pointed out, we need new theories to encompass the demonstrable impact of psychological and social factors on health.

Experience in Toronto

At the Princess Margaret Hospital, we have developed a brief group therapy program which includes the kinds of intervention claimed to be useful in helping to combat cancer: Relaxation, meditation, mental imagery, and self-awareness, e.g., how to handle stress, and defining and working towards goals. All these techniques are in general use by clinical psychologists and psychiatrists, and only somewhat radical element being the use of visualization of tissue changes. Our patients have all received regular medical treatment. Groups of about 10 people meet for one and

one-half hours per week for seven weeks, and individuals do considerable home practice with the aid of audiotapes. Follow-up discussion and support groups are held for "graduates" of the course, and more advanced groups are being instituted.

Over the last three years, 110 patients, plus a small number of spouses and health professionals, have taken the course. Attendance rate (over 80%) and compliance with the homework has been high. Our first aim has been to show that this kind of therapy alleviates psychological distress, especially anxiety and depression, and the results of standard questionnaires given before and after the course show that this happens for most participants. The long-term goal is to gain experience with the kinds of psychological change that correlate with good medical progress. It is already evident that these "self-help" techniques can bring about profound changes in attitude and lifestyle, and our preliminary impression is that patients who do well medically often are among those most involved with their meditation and imagery. Our experience with these individuals, and encounters with other patients who have had unexpected recovery from cancer, supports published descriptions of such people: They show high ego strength and will to live coupled with acceptance of some responsibility for their healing and a belief that it can occur; they undergo healthy changes in lifestyle and often have an increased sense of purpose in life which frequently is associated with spiritual development. In the *New England Journal of Medicine*¹⁴, Dr. Robert Mack, a surgeon who apparently underwent many such changes in his own fight against cancer, writes: "I believe that each of us can affect our own life and health, perhaps even our death, through our attitudes towards life and toward the treatment we are undergoing".

Needs for the Future

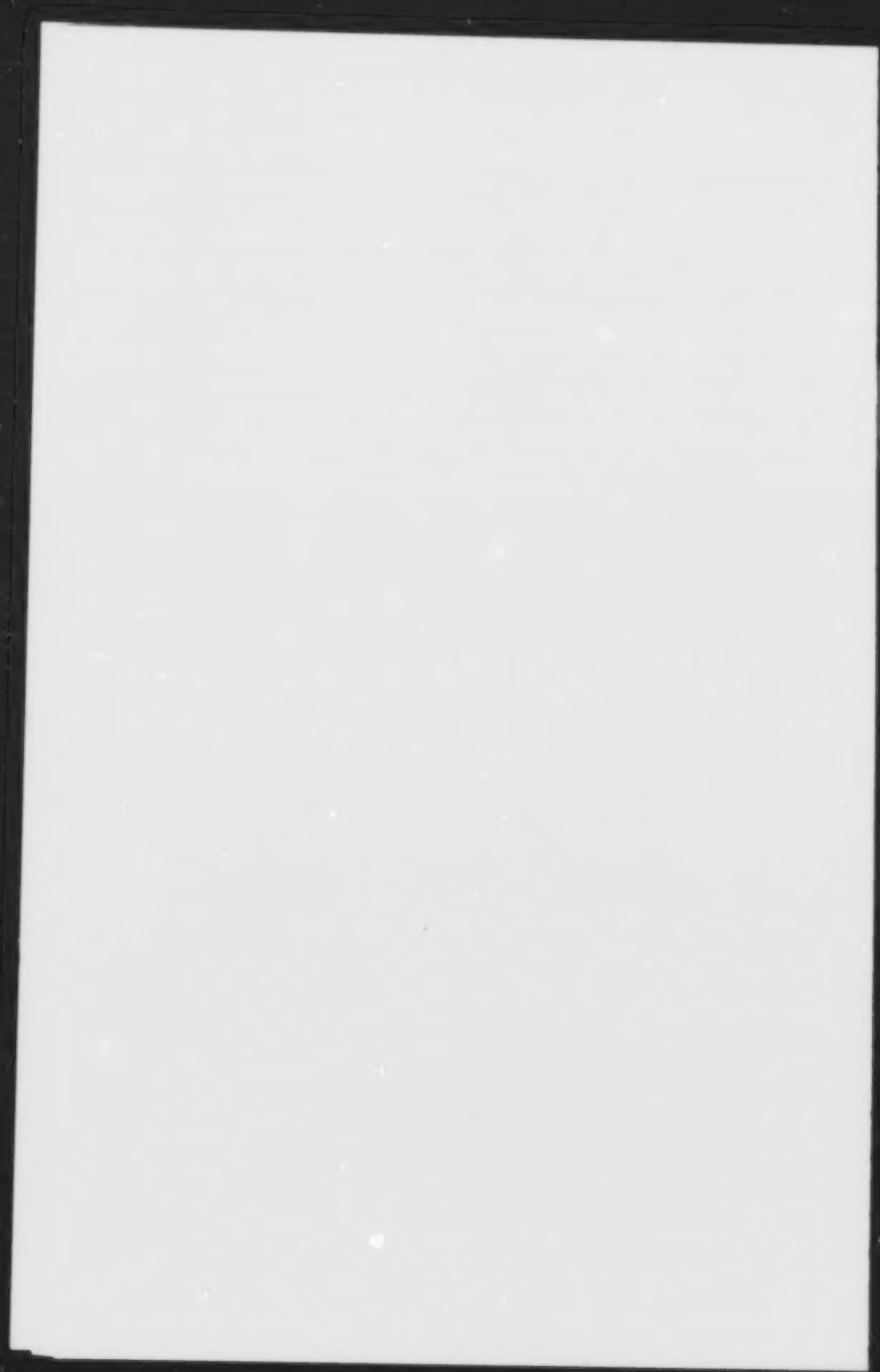
There is now an urgent need for controlled clinical trials of adjunctive psychological therapy in cancer, not only to uncover any possible benefits, but also to resolve an awkward situation in which many patients ask for a kind of treatment that most physicians do not know about or endorse. The ideal experiment would be to recruit a large group of patients, and assign them randomly to two smaller groups, only one of which would receive psychotherapy. Grossarth-Maticek¹⁵ has done this with his individual therapy although he claims only a small prolongation of life. However, with the techniques that have been used in North America and for which its proponents have claimed some long-lasting remission of disease, a great deal of the impetus must come from the patients themselves. The major limitation seems to be that only a small proportion of cancer patients are sufficiently motivated to do enough work to have a chance of achieving observable differences in their disease. True individual progress might be obscured when group averages are considered. In practice, then, we need to work mainly with the few, highly motivated people; this selectivity makes it difficult to perform the "ideal" experiment. It may be necessary instead to build up gradually a correlation between mental changes and medical outcome, comparing these patients with carefully matched controls who do not use the psychological techniques. As the value of these methods becomes clear, they

should appeal to a wider range of patients and physicians, leading to a wider exploration of their use with many chronic diseases.

Finally in this work it is vital to be sensitive to patients' existing coping mechanisms. The therapist has to tread carefully along a narrow path: On the one hand, he must avoid any imputation of guilt if people do not do as well as they hope and, on the other hand, he must maintain a sufficiently high level of enthusiasm and realistic hope to motivate patients towards effort and change.

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EDUCATION



SUMMARY OF OCTRF EDUCATION ACTIVITIES

Manpower Shortage of Oncologists in Ontario

The report of the consultants engaged to conduct a Provincial Role Study of the Ontario Cancer Institute and the Ontario Cancer Treatment and Research Foundation, which is due shortly, is expected to suggest future directions for these two organizations. Of importance is the shortage of oncologists in Ontario (particularly radiation oncologists) and the changes in education which will be required to guarantee an adequate output of these medical specialists. The Province needs numbers sufficient to meet the demands for clinical service, to carry on research and to provide education which are essential to ensure the provision of high quality care for Ontario's cancer patients. During this past year, Queen's University and the University of Western Ontario responded to these needs when they allocated "add-back" residency positions in oncology beginning in July 1985. These positions will complement earlier commitments by the University of Toronto, McMaster University and University of Ottawa.

The Foundation continues to fund a minimum of three training posts in oncology (preferably radiation oncology) at each of its regional cancer centres associated with medical schools; however, this is a "stop-gap" measure only and this level of support will not necessarily ensure sufficient numbers of radiation oncologists.

Undergraduate Medical Education

No significant change has occurred in the medical schools with respect to the exposure of medical students to the multidisciplinary management of cancer as carried out in the regional cancer centres, via compulsory clinical clerkships, for example. Once the Role Study report is received, it is likely that the Foundation's Sub-Committee on Undergraduate Medical Education will be re-activated.

Ivan H. Smith Memorial Studentships

In 1984, in co-operation with the Canadian Cancer Society Ontario Division, the Foundation awarded 21 studentships for periods of 4 to 12 weeks. All studentships were taken outside of the academic year rather than as an elective at the following regional cancer centres: Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, Windsor; and at the Princess Margaret Hospital.

The Ivan Smith program helps to expose medical undergraduates to oncology in the regional cancer centres; however, it is apparent from the limited numbers of students choosing to specialize in oncology that a concerted organized effort is required by all concerned with the education process to increase the numbers of students entering the oncology field.

Postgraduate Medical Education

The Foundation's Sub-Committee on Postgraduate Medical Education did not meet in 1984 because the findings of the Role Study will have a significant impact upon its future role and its interaction with other organizations.

The Harold E. Johns Fellowships in Medical Physics

In 1984, 12 Harold E. Johns Summer Studentships in Medical Physics were awarded and taken in the regional cancer centres in: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview; and at the Princess Margaret Hospital. This program has been funded to date from a special cancer services improvement grant from the Canadian Cancer Society Ontario Division.

In 1984, as in 1983, there was no competition for the Graduate and Post-doctoral Fellowships in Medical Physics established a few years ago in honor of Dr. Harold E. Johns, O.C. Instead the funds were invested in the summer studentships program which all hope, over the long term, will stimulate the entry of medical physicists into oncology.

Dr. W. P. Jeeves, recipient of the first Harold E. Johns Postdoctoral Fellowship in Medical Physics, completed his studies in June 1984 and since has joined the staff of the Hamilton Regional Cancer Centre as a career scientist.

Dr. Michael Patterson, physicist now on the Hamilton Centre staff, was the corecipient of the first Harold E. Johns Graduate Fellowship in Medical Physics. Mr. Michael Wood, the other corecipient of this award, is partially through his fellowship at the Ontario Cancer Institute.

Continuing Professional Medical Education

In 1984, active programs of continuing education were carried out in the regional cancer centres and at the Princess Margaret Hospital through clinical days, seminars, guest lecturers and the lectures in the community by staff members. At the Foundation's Head Office in Toronto, the Division of Epidemiology and Statistics conducted two seminars in epidemiology. These sessions provided a valuable exchange of information and views among epidemiologists from across the Province and members of the Foundation staff.

Foundation grants to Ontario's medical schools supported a number of postgraduate programs with a significant cancer content.

On October 18, 1984, the Toronto-Bayview Regional Cancer Centre was the host for the Foundation's 23rd Clinical Conference. Held at the Inn on the Park, Toronto, the conference addressed the topic of "The Treatment of Localized Hodgkin's Disease and Non-Hodgkin's Lymphoma" (see summary of papers in this section).

On October 1-2, 1984, the Ottawa Regional Cancer Centre co-operated with the Ottawa Regional Hyperthermia Group to organize a hyperthermia workshop on the topic "Physical, Biological and Clinical Aspects of Hyperthermia".

Dr. Robert W. Bruce, Director of the Ludwig Institute for Cancer Research —

Toronto Branch, delivered the 1984 W. G. Cosbie Lecture during the annual meeting of the Canadian Oncology Society in Montreal, September 11-13, 1984. His subject was "Relationship between Diet and Colon Cancer: Laboratory and Clinical Studies".

On March 9, 1984, Dr. Larry Nathanson, Director of Oncology-Hematology, Nassau, Mineola, New York, delivered the 1984 Eleanor Leder Fund Lectureship in Oncology. He spoke on "Randomized Clinical Trials: Physician as Investigator/Physician as Therapist", at the University of Toronto. The lecture and the panel discussion, which followed, were videotaped and the tape is available to the professional community through Dr. Kathryn M. Taylor, Department of Behavioural Science, University of Toronto.

On September 21, 1984, Dr. P. Branton gave an Ontario Cancer Foundation Lecture entitled "Human Oncogenes", at the annual meeting of the Ontario Association of Pathologists, held at the Royal Connaught Hotel in Hamilton.

On October 19, 1984, the Foundation, through a grant-in-aid, supported a program on oncology-palliative care at the 22nd Annual Scientific Meeting of the Ontario Chapter, College of Family Physicians of Canada, held in Toronto. At the meeting, Dr. John Scott, Director, Palliative Care, Women's College Hospital, Toronto, spoke on "Anodynes for Malignancy", and Dr. Michael Jewett, Urologist, the Wellesley Hospital, Toronto, spoke on "Testicular Cancer and TSE (testicular self examination)".

The 1984 Bert MacLaren Lecturer was Dr. T. P. Miller, Section of Hematology/Oncology, University of Arizona, Tucson. On October 18, 1984, at the 23rd Clinical Conference of the Foundation, he gave a lecture entitled "Treatment by Chemotherapy Alone".

The 1984 exchange visitor sponsored under the Joseph J. Schiffer Exchange Program in Oncology was Dr. Nechama Haran-Ghera, Oling Sang Professor of Leukemia Research at the Weizmann Institute of Science, Israel. This program is sponsored jointly by Mount Sinai Hospital and the Foundation.

The Harold G. Vail Visiting Professorship Fund at the Ottawa Regional Cancer Centre supported a visit from Dr. Philip Rubin, Professor of Radiation Oncology at the University of Rochester. Dr. Rubin spoke on "Hodgkin's Disease: Is there a Price for Successful Treatment?"

Last year we reported that a Directory of Cancer Services for Metropolitan Toronto is being compiled, which will list the many aids, techniques, services and benefits available to cancer patients. The directory will be circulated widely in the community, especially to physicians, other health professionals, referral agencies and libraries. The first draft of the Metropolitan directory will be completed by March 1985. Envisioned as the prototype for Ontario, the directory will be reviewed by referees chosen by the Executive Director of the Foundation. Following revision and before publication, it will be distributed to sponsoring agencies. It is interesting to note that the process of gathering data from the providers of these services has stimulated much of the cancer care community to take a fresh look at its activities.

Public Education in Cancer

The Standing Committee on Procedural Affairs of the Legislative Assembly, when it reviewed the Foundation in September 1983, made recommendations concerning education in cancer which have been acted upon as follows:

With respect to its role in public education, the Foundation has undertaken a two-year pilot Cancer Information Service, centred at the Hamilton Regional Cancer Centre. This project, which began on November 1, 1984, is funded jointly by the Canadian Cancer Society Ontario Division and the Foundation.

Regarding its co-ordinating role in education of elementary school children with regards to health hazards of smoking, the Foundation staff have met with representatives of the Canadian Cancer Society Ontario Division, the Ministry of Health, and the Ministry of Education to explore the ways to promote such education. To date, however, a specific course of action has not been identified. More recently, we met with representatives of the Addiction Research Foundation and the Office of Health Promotion of the Ministry of Health to consider further action.

Mary Lou Erochko

RELATIONSHIP BETWEEN DIET AND COLON CANCER: LABORATORY AND CLINICAL STUDIES

W. G. COSBIE LECTURE 1984*

W. R. BRUCE, M.D., Ph.D.**, *Toronto, Ontario*

The origin of colon cancer remains a mystery. While epidemiological studies show that diets high in fat and low in cereal grain products are associated with an increased risk for the disease, they give no indication of the specific carcinogen responsible. This situation may change soon. The use of new toxicological methods to study body fluids and the application of the flexible endoscope to study the colon wall and its response to dietary changes have made it possible to identify candidates (for the carcinogen responsible for colon cancer) and to devise methods for assessing the relative importance of each. This paper will describe briefly four approaches to the search for the cause of bowel cancer.



In 1975 Ames described a method for detecting chemical carcinogens¹ that was based on the supposition that initiators of cancer were mutagens. The test detected chemicals that could induce back-mutations in a particular strain of *Salmonella* under defined conditions which included the presence of a P450 activating system. This simple test, which has been successful at identifying carcinogens, has been used by many scientists to ascertain risks in the environment. It can define possible hazards in water and air pollution, in industrial chemicals and in cosmetics.

We have used this short-term test for carcinogens in a different way. Since our problem was cancer of the colon, we looked for possible carcinogens in human feces. We soon found that many people pass feces, which contain mutagens, and organic extracts of the feces from these individuals did give rise to mutations on the tester organisms. Furthermore, chromatographic purification of these extracts gave rise to fractions that were highly mutagenic. It took much longer to determine the exact structure of the fecal mutagen. My associates, Drs. I. Gupta and J. J. Krepsky,

*Abstract of a paper presented at the annual meeting of the Canadian Oncology Society, held in Montreal, P.Q., September 11-13, 1984.

**Director, Ludwig Institute for Cancer Research — Toronto Branch.

worked with over a ton of fecal samples to isolate enough pure compound to establish its structural identity². Isolation was difficult because the compound was sensitive to light, oxygen and acid. Indeed, the pure compound had a unique and interesting structure: it was an ether in which a glycerol was linked with an unsaturated long-chain alcohol. The alcohol had five conjugated double bonds so we called this mutagen "fecapentene".

Quite a little is now known about the fecapentenenes. They are more frequent in the feces of individuals on Western diets than in those on rural African diets. They are made by certain strains of the *Bacteroides* family. Their concentrations are reduced by supplementary dietary ascorbic acid (Vitamin C) and alpha-tocopherol (Vitamin E). They are presumed to be alkylating agents because of the way in which they form carbocations. However we do not know yet whether these compounds are responsible for colon cancer.

In our second approach, we looked for chemicals that could act as initiators of carcinogens for bowel cancer, by examining the colons of experimental animals after they had been given known colon carcinogens. As had been described earlier by the Belgian pathologist, Maskens, we found that these carcinogens produced a marked degree of nuclear damage at the bottom of the colonic crypts³. Because these nuclear aberrations were easy to quantitate, they became the basis of a simple screening test for colon carcinogens⁴; in a similar way my colleague, Dr. J. A. Heddle, has used micronuclei in bone marrow to screen for chemicals that act there⁵.

The nuclear aberration test was applied to a number of possible sources of carcinogens. Dr. R. P. Bird found that the mutagens created during the cooking of meat increased the levels of these aberrations⁶. Dr. K. Suzuki found that components of human feces also contained compounds that produced nuclear damage⁷. The structure of these compounds have not yet been defined precisely but it seems likely that they are cholesterol oxidation products. It will be interesting to determine whether indeed they are colon carcinogens.

The study of bile acids provided a third approach to the identification of possible carcinogenic factors. Previous investigators have shown that bile acids, such as deoxycholic acid, could act as promoters of the carcinogenic process in the colon⁸, and many workers have noted the deleterious effects of these acids on the colon wall. In man, bile-acid perfusion produces a significant loss of cells from the colonic epithelium and a significant increase in the permeability of the colonic mucosa⁹.

When my colleagues, Dr. M. J. Wargovich and Mr. H. L. Newmark, and I first witnessed this phenomenon we were impressed by its similarity to the damage by the calcium binder, EDTA. Then we wondered whether the damage produced by the bile acids could be modified by calcium, and whether the addition of calcium would block the damage. We found that oral calcium, as a simple salt, was capable of blocking the damaging effects of deoxycholic acid. We postulated that, when they were in their ionized forms in solutions, bile acids and fatty acids could act as promoters of colon cancer in man but that they became inactive when the diet supplied sufficient calcium to precipitate these acids as their calcium soaps¹⁰. Again

we do not know yet whether this hypothesis is correct.

It is one thing to develop an hypothesis and another to test the hypothesis and show that it can lead to a method for preventing cancer. Colon cancer develops in only a few of us and probably only after a long exposure to carcinogenic chemicals. The task is to find ways to test these different hypotheses in small groups of patients observed only for short periods. Our approach came from reviewing the pathology studies of Dr. B. Morson and his collaborators; these workers had shown that most colon cancers do not arise *de novo* but through the adenoma-carcinoma sequence¹¹. That is, most tumors develop from or are associated with colonic polyps, which appear in most adults on a Western diet before they reach the age of 60. Thus we decided that we could simplify our search by looking for conditions that reduce the frequency of polyps. If we could prevent these polyps, presumably we could reduce the risk of colon cancer.

At the moment, my colleague, Dr. G. McKeown-Eyssen, is carrying out two clinical studies aimed at determining whether dietary changes can affect the development and growth of new polyps in individuals at risk for polyp growth¹². These studies are being done in collaboration with a number of gastroenterologists and surgeons working in Toronto hospitals and clinics. The first of these trials is directed at determining the importance of ascorbic acid and alpha-tocopherol supplementation in the diet. These antioxidants reduce the levels of fecapentenes and presumably would have a similar effect on cholesterol oxidation products. The second trial is designed to assess the effect of fat reduction and fiber supplementation — an intervention that should lower the levels of soluble bile acids and fatty acids in the colonic stream.

The studies described briefly here indicate the range of methods now available for the study of the origins of colon cancer. Given sufficient diligence and patience, we should be able to define the factors which lead to colon cancer and to map out direct approaches to the prevention of colon cancer.

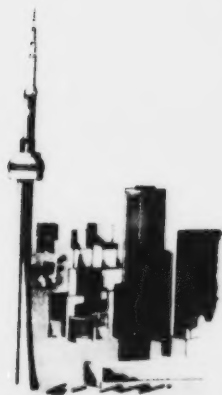
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23rd CLINICAL CONFERENCE

THE TREATMENT OF LOCALIZED HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA



The 23rd Clinical Conference of the Ontario Cancer Treatment and Research Foundation provided a state-of-the-art review of the management of localized lymphomas for some 220 registrants. For the morning session on Hodgkin's disease, the principle speakers included Dr. Richard Hoppe (Stanford University), Drs. Derek Jenkin and James Rusthoven (Toronto-Bayview Centre), Dr. Marilyn Sonley (Hospital for Sick Children, Toronto), and Drs. Daniel Bergsagel and Simon Sutcliffe (The Princess Margaret Hospital, Toronto). The afternoon speakers on non-Hodgkin's lymphoma included Dr.

Bharat Nathwani (University of California), Dr. Derek Crowther (University of Manchester), Dr. Thomas Miller (University of Arizona), Dr. Mary Gospodarowicz (The Princess Margaret Hospital), and Dr. William Hryniuk (Hamilton Regional Cancer Centre). The morning session was chaired by Dr. David Osoba (Toronto-Bayview Regional Cancer Centre) and summarized by Dr. Raymond Bush (The Ontario Cancer Institute). The afternoon session was chaired by Dr. Donald Cowan (Sunnybrook Medical Centre) and summarized by Dr. Haydn Bush (London Regional Cancer Centre). The following summaries include data presented at the conference.

(A detailed account of this conference has been submitted for consideration of publication to the *Canadian Medical Association Journal*.)



Participants at the conference, left to right: Drs. D. Crowther, T. P. Miller, R. D. T. Jenkin, R. T. Hoppe and B. D. Nathwani.

EARLY-STAGE HODGKIN'S DISEASE: A REVIEW OF CURRENT TREATMENT APPROACHES*

J. J. RUSTHOVEN, MD **, *Toronto, Ontario*

The treatment of Hodgkin's disease (HD) has been a model for the successful eradication of malignant disease in man. Until 1970, nearly 50% of males in Ontario with HD died of the disease; between 1975 to 1980, this figure fell to 25%, and survival improved in all stages of the disease. Fifty years ago, we knew that radiation could cure early Hodgkin's disease. However, this fact was not accepted until the mid-1950s and then chiefly through the pioneering efforts of Dr. Vera Peters. In a review of the experience at the Toronto General Hospital from 1924 to 1942, she showed that 5- and 10-year survival rates of 88% and 79%, respectively, could be achieved for disease confined to a single lymphatic region (Stage I). For Stage II disease (lymphatic disease confined to either side of the diaphragm), 5-year survival remained excellent (72%) but by 10 years only 21% of patients were alive. This reflected the low cure rate achieved with repeat radiotherapy (RT) following relapse.

Dr. Peters' work helped to provide the impetus for further improvements in radiation such as the development of the dose response curve for HD, and the addition of the bipedal lymphangiogram to staging practices in the 1950s. This latter technique and the information obtained by the staging laparotomy with splenectomy has added greatly to our understanding of the prognostic significance of occult disease in the abdomen. It soon became clear that 10% and 20% of patients with clinical Stage I (CS I) disease and up to one-third of patients with supradiaphragmatic CS II disease had at least pathological Stage III (PS III) disease on the basis of occult abdominal disease. Survival rates improved further when large, irregular radiation fields were developed to encompass such occult disease. New 4 and 6 MeV linear accelerators facilitated the application of these large fields which included "mantle" and "inverted Y" fields. Though a few favorable, very early stage presentations can be treated with "involved field" irradiation alone, most early-stage patients require "extended field" irradiation to avoid a high rate of relapse. Using this approach, one can expect a 10-year relapse-free survival and overall survival rates of 80% and 95%, respectively.

Combination chemotherapy (CT) also can cure patients with HD. Since 1964, the combination of nitrosourea, vincristine, procarbazine, and prednisone

*Summary of papers presented at the morning session of the 23rd Clinical Conference, held in Toronto on October 18, 1984.

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(MOPP) has cured about 50% of patients with advanced disease. At present, when combined with irradiation as initial therapy, CT significantly reduces post-radiotherapy relapse rates. In addition, CT can induce complete remission and long-term survival in more than 50% of patients who relapse following initial RT alone. Using either of these approaches to bimodal therapy, one can expect an overall survival of 90% or more at 10 years for CS I and II disease.

Early-stage disease in children has been treated with similar success. However, they run the risk of bacterial infections after splenectomy and suffer impaired growth of bone, especially after extended-field radiation. Better treatment plans are needed to improve the quality of life while maintaining or improving rates of survival.

Radiotherapy for Stage I and II Disease

Initially pathological staging, mainly as laparotomy and splenectomy, was used to gain information useful in the planning and treatment of clinically staged HD. Over time, however, some centres have come to view pathological staging as necessary for treatment and planning.

In pathological staging (to detect occult disease), the information usually is derived from laparotomy and splenectomy, but such staging may refer, for example, to liver biopsy done at laparoscopy. Many centres do laparotomy with splenectomy routinely after thorough clinical staging in medically acceptable patients. Then, radiation fields can be planned according to the known extent of disease and the anatomical changes made at surgery.

Randomized, prospective clinical trials at Stanford and other centres have shown that PS I and II patients require extended-field irradiation if they are to achieve optimal relapse-free survival (77%) and overall survival (84%) at 10 years¹. Involved field irradiation alone is appropriate only for non-bulky, high cervical disease without systemic symptoms. Most authorities recommend total lymphoid irradiation for PS IB and IIB disease, because in these stages, without pelvic irradiation, relapse is frequent enough to justify the increased morbidity associated with total lymphoid irradiation.

With optimal pathological staging and carefully planned irradiation, about 15% of patients still relapse and require further treatment. Among the most important subgroups with higher relapse rates are patients with a large mediastinal mass. Other factors reported to increase relapse rates for PS I and II after RT alone include the presence of hilar disease, systemic ("B") symptoms, "E" lesions (localized disease in a single extralymphatic organ or site), and involvement of more than two nodal sites. For these factors, however, relapse rates usually do not exceed 20-25%. In addition, most centres report no difference in overall survival whether these patients are treated initially with RT alone or combined therapy.

When clinical staging is used and clinical attributes affecting prognosis are considered in treatment planning, the number of patients cured and the overall survival appears to be the same as in patients with the same clinical stage but treated according to their pathological stage. The greater relapse rate in clinically staged

patients is offset somewhat by cures among patients salvaged with CT, hence the same overall long-term survival. Among CS I and II patients treated with radical RT alone on the basis of clinical stage at presentation, workers at the Princess Margaret Hospital retrospectively defined three patient groups based on factors predictive for relapse — age, histology, extent of disease, and systemic symptoms². The 5% of patients, who presented with only upper cervical disease (CS IA), had a cure rate that exceeded 95%. On the other hand, another subgroup (10%) with poor prognostic indicators — age greater than 50, systemic symptoms, mixed cellularity or lymphocyte-depleted histology, had a relapse rate exceeding 70%. The large majority (85%), who had fewer poor prognostic factors, had a relapse rate of 35%. When these groups received subtotal or total nodal irradiation to include infradiaphragmatic disease, the relapse rate fell to 27%. The Toronto group also showed that large mediastinal disease results in unacceptably high relapse rates among CS I and II patients treated with RT alone. However, without the aid of laparotomy, subtotal lymphoid irradiation in CS I and II patients with unidentified extensive splenic involvement may be followed by a significant relapse rate in the pelvis and/or extranodal sites. Though it may still be useful to do a laparotomy to identify this subset of patients for more extensive RT, successful salvage therapy after relapse may make this unnecessary. Thus, because either pathological or clinical staging produces equally good results, the physician or centre may choose one of the approaches depending on the resources available to perform pathological staging, and on the short- and long-term morbidity inherent in the associated treatment strategies.

Less than 10% of patients with early-stage disease present with infradiaphragmatic disease. Though in general, this presentation does not affect overall survival, patients with ilioinguinal disease and a positive lymphogram who are treated with RT alone may be expected to have a high relapse rate. These patients may benefit from initial combined therapy.

Indications for Combined Modality Therapy

Historically, combined (bimodal) therapy — CT plus RT — has been used in patients with early-stage HD who are expected to have unacceptably high relapse rates if treated with RT alone. Today, the choice of bimodal therapy is based on a number of factors which include staging practices, the use of prognostic indicators, and desired therapeutic end-points. These, in turn, depend on local circumstances, e.g. surgeons experienced in performing the laparotomy, and individual treatment philosophy, viz., whether to treat to reduce initial relapse rate, or to accept relapse but to treat again successfully to achieve the same overall survival.

In the early 1970s, Andrieu et al in Paris began prospective clinical trials to answer the question: Can CT, when added to initial RT, eliminate the need for subdiaphragmatic RT and reduce RT fields for bulky disease? They did laparotomy only in patients without systemic symptoms or multiple involved nodal sites to define those who needed more than involved-field RT. To date their results show that giving three courses of MOPP before involved- or extended-field RT gives relapse-free and

overall survival at 7 years of 90% and 94%, respectively, for CS I and IIA disease⁴. CS IB and IIB patients who received six courses of MOPP followed by RT, has a 10-year actual relapse-free survival of 81% and an overall survival of 89% (Table I). This approach aims to reduce the initial relapse rate at the price of associated morbidity. However many centres do not accept this approach, because it reduces radiation-field volume and hence exposes the patient to severe short- and long-term toxicity.

TABLE I

Composite Results of Treatment for Early Stage Hodgkin's Disease

Groups	Stage	Treatment	5 YEARS	
			Relapse Free Survival (%)	Overall Survival (%)
Hagemeister <i>et al.</i> 1982 Nisseau <i>et al.</i> 1982 Hoppe <i>et al.</i> 1982	PS I-II	EF or TL1	66-79	93-96
Hellman <i>et al.</i> 1982 Hoppe <i>et al.</i> 1982 Hagemeister <i>et al.</i> 1982	PS IA-IIA	EF	74-84	94-98
Hoppe <i>et al.</i> 1982	PS IB-IIB	TL1	83	92
Hoppe <i>et al.</i> 1982 Hagemeister <i>et al.</i> 1982		RT + MOPP x 6	84-91	85-100
Tubiana <i>et al.</i> 1984	CS IA, IIA (favorable)	IF or EF	81-84 (4 yrs)	97 (4 yrs)
Andrieu <i>et al.</i> 1980		MOPP x 3 + RT	90	94
Tubiana <i>et al.</i> 1984	CS IB, IIB (unfavorable)	TL1	75 (4 yrs)	90 (4 yrs)
Andrieu <i>et al.</i> 1984		MOPP x 3 or 6 + RT	81 (10 yrs)	89 (10 yrs)

Another approach, used at Stanford, M.D. Anderson Hospital, and other centres, employs pathological staging more extensively, but in conjunction with clinical prognostic factors. Although some groups base treatment policy in part on factors which predict initial relapse, others have attempted to define factors which predict to a second relapse. Here they hope to determine which subgroups of patients, having relapsed after RT alone, will have a decreased overall survival after initially successful salvage therapy. Then these patients would receive bimodal therapy as their initial treatment. The Stanford group uses bimodal therapy for patients presenting with a large mediastinal mass who respond poorly to the first 1500-2000 cGy of mantle-field RT. Since, despite a high relapse rate, the overall survival for this subgroup as a whole is not different whether RT or combined modality therapy is used initially, combined modality therapy is used here to treat only poor RT responders whose overall survival may be reduced following initial RT alone. Recently, Schomberg *et al.* at the Mayo Clinic cautioned against the initial use of combined modality therapy for this subgroup as a whole because their recent

retrospective review showed excellent salvage rates⁵.

On the other hand, Hagemeister et al at M.D. Anderson Hospital found that extended-field RT and involved-field RT followed by six courses of MOPP both were associated with reduced relapse-free survival and overall survival at 5 years in patients with a large mediastinal mass (greater than 7.5 cm)⁶. These reductions were only significant, however, when hilar disease was present. Systemic symptoms were a poor prognostic factor but were not independent of mediastinal involvement. Other factors which may adversely affect overall survival are age greater than 40, more extensive disease at initial presentation, and splenic involvement identified at relapse.

Ultimately with this approach the issue becomes: How do we identify those few patients who need combined modality therapy so as to spare the large majority of patients the morbidity of this treatment? In their most recent study the EORTC addresses this question by using overall survival as the endpoint to treatment success. Using clinical staging and prognostic factors to define a large "unfavourable" group, they found that combined modality therapy significantly improved the relapse-free survival at 4 years compared to TN1 (total nodal irradiation), but did not affect overall survival⁷. Though the follow-up after relapse is short, other groups agree that at least 60% of patients relapsing after RT alone can expect long-term freedom from second relapse following salvage chemotherapy.

Table II lists the subgroups which may benefit from combined modality therapy compared to RT alone.

TABLE II

Subgroups Considered for Initial Bimodal Therapy

Staging Approach	Subgroups	Outcome Parameter Improved by Bimodal Therapy
Pathological	Large mediastinal mass ± hilar disease	RFS and/or FF2ndR
	Systemic symptoms	RFS
	Extensive splenic disease	RFS
	Paraortic involvement	FF2ndR
Clinical	Large mediastinal mass	RFS
	Splenic involvement	RFS
	Age greater than 40	FF2ndR

Late Effects of Treatment

Adequate treatment for early-stage disease still exacts a high price. Though uncontrolled HD is still a frequent late complication, especially in poorer prognosis patients receiving RT alone, other important complications are sterility, second malignancies, and infection⁸. Sterility is mainly a consequence of chemotherapy and men treated with MOPP may develop permanent oligo or azoospermia. Though HD itself predisposes to poor sperm number and function, clearly this is exacerbated by MOPP. A recent study suggests that treatment with 3 or fewer courses of MOPP may result in higher sperm counts than after treatment with 5 or more courses⁹. In women receiving pelvic RT and no chemotherapy, menses and fertility can be preserved by oophoropexy and appropriate ovarian shielding (by this method, the dose to the ovaries is less than 250 rads). Among women receiving MOPP, those older than 20 years have an increasing frequency of oligo and amenorrhea with the latter approaching 100% by age 35. Usually women less than 20 years of age continue regular menses. The effects of RT and CT on fertility are at least additive and the final outcome may be delayed for up to 2-3 years.

Second malignancies occur primarily following programs which contain CT. The two most frequently reported second tumors are acute non-lymphocytic leukemia (ANLL) and non-Hodgkin's lymphoma (NHL). Stanford and the NCI group reported no increased risk of ANLL after RT alone¹⁰. In large series of patients receiving CT, the actuarial risk of ANLL at 10 years varies from 2-6% and increases to 6-7% in patients receiving combined modality therapy. The risk seems to be similar in patients receiving CT as part of combined modality therapy, and compared to those requiring CT for salvage only. The increased risk with CT is higher for patients over age 40 or 50, with a 10-year actuarial risk of 13% and 21% in two recent series. No one yet knows whether adjustments in the sequencing of each modality will reduce this risk. Patients developing ANLL in this setting have a median survival that is measured in months. The actuarial risk of NHL is high, reported to be 4.4% at 10 years by two groups¹¹. For those receiving combined modality therapy, the risk may be as high as 15%. Characteristically these lymphomas have a diffuse pattern with a higher or intermediate grade and have a high incidence in the gastrointestinal tract. Unlike ANLL, these tumors tend to be equally represented in all age groups. Other solid tumors seen as second malignancies include lung carcinoma and sarcoma. Newer CT such as ABVD (Adriamycin, bleomycin, vinblastine, DMC) appears to be at least as effective as MOPP when combined with RT but to date seems to be associated with less sterility and fewer second malignancies¹².

Infections most commonly associated with HD include herpes zoster or other viral diseases. The common fungal infections are cryptococcosis, histoplasmosis, and coccidioidomycosis. Treatment-related immunosuppression and splenectomy also predispose to infection.

Notler and his colleagues from Stanford have shown that the risk of infection after relapse was six times the risk before relapse; following splenectomy a peak infection period occurred 30 days after operation¹³.

The complications of radiation include fibrosis which is usually localized, thyroid dysfunction, and chronic pericardial disease.

Future Considerations

Despite the excellent results now achieved in early-stage disease with RT, CT or both, problems remain. We need to determine whether laparotomy-based information is essential in treatment planning; now the EORTC is addressing this problem prospectively in their most recent clinical trial⁷. Newer CT regimens that are as effective as MOPP in various treatment settings (PAVe¹⁴, ABVD¹²) may be better tolerated (PAVe) or have fewer short- and long-term adverse effects (ABVD). Other regimens have been used to improve second and even third remission rates (CEP)¹⁵ in relapsed patients. More trials are needed to confirm the efficacy of these newer regimens, with the goal of equalling or improving on the relapse-free and overall survival achieved with MOPP while reducing long-term morbidity. Future treatment philosophies should also consider the results of prospective assessments of quality-of-life parameters. With improved freedom from second relapse, the most intensive treatment could be reserved for relapsed patients requiring retreatment with CT; if, in turn, newer salvage CT is less morbid, most patients can be spared the significant long-term complications presently related to CT.

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THE CURRENT MANAGEMENT OF LOCALIZED NON-HODGKIN'S LYMPHOMAS*

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The non-Hodgkin's lymphomas are a heterogeneous group of disorders with a wide variation in clinical presentation, biologic aggressiveness and response to therapy. This variation in clinical behaviour holds true for both the localized (Ann Arbor Stage I and Stage II) and disseminated forms of the disease. Truly localized disease is uncommon and, as a result, no one institution has been able to accumulate a broad experience. Over the last decade new developments in histopathology and immunology and an increasing number of clinical studies provide the data base to guide the clinician in the management of these disorders.

Pathologic Classification

For 25 years the classification system most widely used in North America was that proposed by Rappaport¹ — a system based entirely on morphologic criteria applied to the involved lymphoid tissue; it emphasizes the predominant cell type — lymphocyte or histiocyte, the degree of cellular differentiation, and the overall architectural pattern — nodular or diffuse. Numerous retrospective studies have confirmed the clinical validity of the Rappaport system^{2,3}. Nonetheless, this classification has undergone significant modification with increasing clinical experience and the evolution of new concepts in histopathology. For example, it is now well established that the diffuse "histiocytic" lymphomas are a heterogeneous group, which can be subdivided into categories with distinct clinical, morphologic and immunologic characteristics. Moreover, most of these tumors are of lymphoid rather than histiocytic origin⁴.

Since 1974, five additional classification schemes have been proposed to overcome the inaccuracy of the Rappaport system. Two of these (the Lukes-Collins system and the Kiel classification) have incorporated immunological concepts, which were unknown when the Rappaport system was proposed. The confusion and controversy generated by six different classification schemes for non-Hodgkin's lymphoma prompted the NCI to conduct an international multi-institutional clinicopathologic study⁵. Six expert pathologists, each a proponent of a major classification, and six experienced pathologists (not identified with one of the major systems) reviewed 1175 cases to assess the reproducibility and clinical relevance of the six major

*Summary of papers presented at the afternoon session of the 23rd Clinical Conference, held in Toronto on October 18, 1984.

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classifications. In the end all six were found to be reproducible and to offer useful clinical correlations. No one system was found to be clearly superior to the others.

To facilitate the comparison of treatment results based on the six major classifications, the participants in the NCI study devised a working formulation⁵. In essence, non-Hodgkin's lymphomas were divided into three major prognostic groupings labelled "low", "intermediate" and "high-grade". These groupings were further subdivided into three or four major subtypes, characterized by a distinctive clinical course and easily recognized pathologic criteria. Table I compares the working formulation classification with the modified Rappaport system. Table II presents the clinical characteristics of the 1014 patients represented by the 10 subtypes of this classification.

Because it chose to exclude immunologic data, the working formulation might be regarded as outdated at the time of publication. Recent immunologic studies of cell-surface markers indicate clearly that non-Hodgkin's lymphomas may be of B-cell or T-cell origin. Those demonstrating no surface markers at all are labelled "null-cell". So far these marker studies have had limited clinical relevance, but they have been useful in distinguishing the clonal status of a malignant population from the polyclonality of a reactive lymphocytic infiltrate. In addition, they are also proving to be useful in prognostication and selection of therapy. For example, it is now recognized that T-cell lymphoblastic lymphoma is a distinct clinical pathologic entity requiring aggressive multidrug chemotherapy⁶.

Do cell surface marker studies add anything to the prognostic information provided by the current morphologic classifications? After all, it is possible to correlate these immunologic markers with cell morphology⁴. For example, one can predict on the basis of morphology alone, the B-cell origin of the follicular-centre cell tumors, the small lymphocytic and the large-cell lymphomas with plasmacytoid features. Similarly, the histologic appearance of some lymphomas suggest T-cell lineage. On the other hand, in the 30% of "histiocytic" lymphomas that appear to be null-cells, there is no consistent correlation between morphology and immunology. In a univariate analysis, Bloomfield⁷ has shown that these markers have prognostic importance, and has shown that the application of cell-surface markers to a major pathologic classification (Lukes-Collins) enable her to identify groups of lesions with clearly different responses to therapy. At the present time it is recommended that non-Hodgkin's lymphomas be classified according to the working formulation classification and also characterized by their cell surface markers.

The Role of Primary Radiotherapy

Historically, radiotherapy (RT) alone has been used to treat patients with localized non-Hodgkin's lymphomas. The evaluation of RT has been hampered because pretreatment staging was not uniform and the various series used different pathological classifications. Retrospective reviews have identified age, stage, bulk of disease, presence of B symptoms and histologic subtype as of prognostic importance; of these, histologic subtype and stage appear to be the most important variables.

TABLE I¹

**A Working Formulation of Non-Hodgkin's Lymphoma
for Clinical Usage: Recommendations of an Expert
International Panel; Comparisons to the Rappaport Scheme**

	WORKING FORMULATION	RAPPAPORT TERMINOLOGY
LOW GRADE		
A.	Malignant Lymphocytic Small Lymphocytic consistent with chronic lymphocytic leukemia plasmacytoid	Diffuse well differentiated lymphocytic
B.	Malignant Lymphoma, follicular Predominantly small cleaved cell diffuse areas sclerosis	Nodular poorly differentiated lymphocytic
C.	Malignant Lymphoma, follicular Mixed, small cleaved and large cell diffuse areas sclerosis	Nodular mixed lymphocytic histiocytic
INTERMEDIATE GRADE		
D.	Malignant Lymphoma, follicular Predominantly large cell diffuse areas sclerosis	Nodular histiocytic
E.	Malignant Lymphoma, diffuse Small cleaved cell	Diffuse poorly differentiated lymphocytic
F.	Malignant Lymphoma, diffuse Mixed, small and large cell sclerosis epitheloid cell component	Diffuse mixed lymphocytic-histiocytic
G.	Malignant Lymphoma, diffuse Large cell cleaved cell non-cleaved cell sclerosis	Diffuse histiocytic
HIGH GRADE		
H.	Malignant Lymphoma Large cell, immunoblastic plasmacytoid clear cell polymorphous epitheloid cell component	Diffuse histiocytic
I.	Malignant Lymphoma Lymphoblastic convoluted cell non-convoluted cell	Diffuse lymphoblastic
J.	Malignant Lymphoma Small non-cleaved cell Burkitt's follicular areas	Diffuse undifferentiated

¹Reproduced from: DeVita VT, Jr., Hellman S: Hodgkin's disease and the non-Hodgkin's lymphomas. In: Cancer: Principles and practice of oncology. Philadelphia: J. B. Lippincott Co., 1982.

TABLE II'
Clinical Characteristics of 1014 Patients in the Ten Subtypes of the Working Formulation of
Non-Hodgkin's Lymphomas for Clinical Usage

PROGNOSTIC GROUP	LOW GRADE			INTERMEDIATE GRADE			HIGH GRADE			
	SL	FSC	FM	FL	DSC	DM	DL	IBL	LBL	SNC
Subtype	A	B	C	D	E	F	G	H	I	J
Study code										
No. in group	41	259	89	44	79	77	227	91	49	58
%	3.6	22.5	7.7	3.8	6.9	6.7	19.7	7.9	4.2	5.0
Age range (yrs.)	26-79	3-87	26-99	16-82	10-91	22-90	10-88	10-81	11-90	3-90
Median	60.5	54.3	56.1	55.4	57.9	58.0	56.8	51.3	16.9	29.8
Sex ratio (M:F)	1.2	1.3	0.8	1.8	2.0	1.1	1.0	1.5	1.9	2.6
Pathologic stage (%)										
I	3	8	15	15	9	19	16	23	7	13
II	8	10	12	12	19	26	30	29	20	21
III	8	16	28	15	12	13	10	16	2	9
IV	81	66	46	58	60	42	44	33	72	57
Bone marrow involved*	71	51	30	34	32	14	10	12	50	14
Survival										
Median (yrs.)	5.8	7.2	5.1	3.0	3.4	2.7	1.5	1.3	2.0	0.7
5-year (%)	59.0	70.0	50.0	45.0	33.0	38.0	35.0	32.0	26.0	23.0
Complete remission (%)	61	73	65	61	56	69	59	53	69	48
Median time to relapse (yrs.)	>5.4	5.0	5.2	>8.0	2.1	4.3	>8.4	3.5	1.1	>7.7
*At initial evaluation										

'Reproduced from: *Cancer* 1982; 49: 2122.

Low-Grade Lymphomas. Clinically staged patients treated with RT for localized low-grade lymphomas can achieve a five-year, disease-free survival of 60%. Pathologically staged patients appear to do even better. The actuarial disease-free survival curves at Stanford plateaued after five years suggesting that a proportion of patients were cured. Multivariate analysis indicated that age and extent of radiotherapy fields were of prognostic importance. Total lymphoid irradiation achieved a longer disease-free survival than did involved field or extended field; this is not surprising because such patients often relapse in contiguous unirradiated nodes. However, a prospective randomized study at Stanford, which compare involved field and total lymphoid irradiation in pathologic Stage I and II showed no statistically significant difference in 5-year disease-free survival (88 versus 100%).

A careful retrospective review of 145 patients with CS I - II low grade non-Hodgkin's lymphomas treated at the Princess Margaret Hospital between 1967 and 1978 identified three independent prognostic variables, namely stage, age and bulk. The adjusted relative death rate was similar for Stages IA and IIA localized but was markedly higher for those with Stages IIA extensive or IB-IIB disease. Increasing age was associated with an increased rate of death from disease. The risk was least for those less than 60 and greatest for those over the age of 70. Finally, the relative rate of death from disease seemed to be highest for those with large bulk and least for those with small bulk disease. This was true whether the pattern of disease was nodular or diffuse.

On the basis of this analysis, the Princess Margaret Hospital recommends that radiotherapy be considered the treatment of choice for localized, low-grade non-Hodgkin's lymphomas. Although the prognosis for some of these patients is poor, there is not better therapy. Chemotherapy has not been shown to cure the low-grade lymphomas.

Intermediate and High-Grade Lymphomas. Few reports in the literature have attempted a separate analysis of the intermediate and high-grade lymphomas; indeed, most reports are dominated by data for diffuse histiocytic lymphoma. The results achieved with RT are quite good: Extended field - total lymphoid irradiation provides a three-year, disease-free survival of 89-100%, compared to 46-75% for involved - external field RT. Without exception the results of treatment in pathologic Stage II are worse than those in pathologic Stage I. The three-year disease-free survival ranges between 0 and 33% for involved field - extended field RT, compared to 50% for extended field - total lymphoid RT.

Few studies have attempted a multivariate analysis of prognostic factors in patients with intermediate and high-grade lymphomas. The Princess Margaret Hospital conducted such an analysis on 337 patients with clinical Stage I-II disease and found that stage, age and bulk were the important prognostic factors.

There is no universal agreement concerning the best therapy for localized intermediate and high-grade lymphomas. Several centres recommend extended field - total lymphoid irradiation for pathologic Stage I disease. The Princess Margaret

Hospital considers patients less than age 60 with small-bulk clinical Stage IA-IIA localized disease to be suitable candidates for primary radiation. In other classes of localized intermediate and high-grade lymphomas, the results with radiation alone are poor and this justifies a trial of chemotherapy.

Extranodal Presentations. Up to 25% of patients presenting with non-Hodgkin's lymphomas will have extranodal disease⁸. In approximately one-third of such cases, this is confined to the head and neck with the majority having involvement of Waldeyer's ring⁹⁻¹¹.

Many series have suggested that there is no significant difference in relapse-free survival between localized nodal and localized extranodal non-Hodgkin's lymphoma. However, there may be a subset of extranodal presentations which do better, namely, the tumors arising from the gut-associated lymphoid tissue (GALT), which include lymphomas of Waldeyer's ring, the thyroid gland and the gastrointestinal tract.

Experience with 139 localized extranodal lymphomas at the Princess Margaret Hospital showed a statistically significant difference in survival between patients with nodal presentations, GALT lymphomas and other extranodal lymphomas. The local relapse rate was similar for all three groups, but differences in distant relapse produced significant differences in overall relapse-free survival. These workers believe that RT alone is inadequate for the non-GALT extranodal lymphomas, even when apparently localized. The outcome for the GALT lymphomas after RT is generally favourable.

The Role of Combined Therapy

Many centres have accumulated considerable experience with chemotherapy, given as an adjuvant to radiation. However, given the small number of patients in individual series, the results are difficult to interpret. In any event, three prospective randomized studies have provided better information.

Bonnadonna¹² compared IF-EF RT to IF-EF RT plus six courses of CVP -- cyclophosphamide, vincristine and prednisone -- in 96 pathologic Stage I-II non-Hodgkin's lymphomas of mixed histology. The five-year overall survival for the whole series exceeded 80% for RT and CVP. The relapse-free survival of 68 patients with diffuse histiocytic (DH) lymphoma approached 70% after RT and CVP. They did not report a breakdown by stage for the subgroup. Nissen *et al*¹³ compared EF RT to EF RT plus chemotherapy -- streptonigrin, vincristine and prednisone given concurrently with RT for six weeks, followed by CVP for three years -- in 73 patients with Stage I-II NHL of mixed histology. With a median follow-up of five years, the group receiving adjuvant chemotherapy had superior disease-free survival (54% versus 10% $p < 0.001$). Subgroup analysis showed this to be also true for the 56 patients with intermediate-grade lymphomas. The advantage was especially striking for the 17 patients with Stage II diffuse histiocytic lymphoma (86% versus 0%).

By way of contrast, Landberg¹⁴ did achieve better relapse-free survival at 30 months in Stage I but not Stage II among 55 patients randomized to nine courses of CVP or no further therapy after a complete remission to EF RT. The 10 patients with DH lymphoma, who received adjuvant chemotherapy, had a better relapse-free survival than the 10 treated with RT alone (100% versus 50%, $P=0.03$). The outcome by stage is not reported for the DH subset.

These studies indicate that patients with localized DH lymphoma achieve superior disease-free survival when treated with radiation followed by adjuvant chemotherapy. Two studies have addressed this question. A prospective randomized study from Manchester¹⁵ compared VAP (vincristine, Adriamycin and prednisone) plus two years of maintenance therapy (6 MP, methotrexate and cyclophosphamide) to six courses of MOPP in 69 patients with unfavourable lymphomas treated initially with radiotherapy. This series specifically excluded low-grade lymphomas and Stage I GALT lymphomas. There was no statistically significant difference between these regimens with respect to complete response rate, actuarial disease-free survival and overall survival for four years.

Bonnadonna¹⁶ did a prospective randomized study of CVP and BACOP as adjuvant therapy in 148 patients with Stage I-II non-Hodgkin's lymphoma of mixed histology. Most of these patients had intermediate and high-grade lymphomas. Three cycles of chemotherapy were delivered before and after IF-EF RT. The complete response rate was similar for both groups. BACOP had a statistically significant advantage over CVP only with respect to the five-year, disease-free survival of the entire group. Analysis by stage and histologic subtype revealed no statistically significant differences between the two arms. As in the Manchester study, bulk was not of prognostic importance. The results of this study can be compared with those from Bonnadonna's earlier adjuvant study in the same group of patients.

The Role of Primary Chemotherapy

The success of adjuvant chemotherapy in improving disease-free survival among patients with localized unfavourable lymphomas has prompted many to ask whether radiation is needed at all.

Concerning the use of CHOP, with or without IF RT, in localized large-cell lymphomas, Miller's experience at the University of Arizona indicates that 7 of 32 patients treated with CHOP have relapsed or failed to achieve a complete response. Twenty patients with comparable disease have been treated with both radiation and CHOP chemotherapy. These patients were selected for radiation if they had limited bone-marrow reserve or if they demonstrated a slow response to chemotherapy. Only two patients in this group have relapsed with a median follow-up of 41 months. The disease-free and overall survival for the entire group of 52 patients was 80% and 83% respectively. Interestingly, a log rank analysis of the entire 52 patients revealed that age, stage, bulk and site of presentation (nodal versus extranodal) was of no prognostic importance in determining disease-free survival. This suggests that effective

systemic chemotherapy may overcome the traditional prognostic variables previously recognized in patients treated with radiation alone. An analysis of the seven "chemotherapy failures" indicates that five failed locally, presumably within an area encompassed by IF RT, if it had been given. Both patients failing after combined therapy did so within the radiotherapy fields.

If chemotherapy is offered as primary treatment for the localized intermediate-grade non-Hodgkin's lymphomas which regimen should be used? The literature contains a small number of reports concerning the results of different regimens in Stage II NHL of unfavourable histology¹⁷⁻¹⁹. To date no regimen is clearly superior.

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During the past year the centre has welcomed several new staff people: Dr. Jadranka Dragovic has joined the Henderson Clinic as a radiation oncologist, and Dr. Alan Neville as a medical oncologist. Dr. Andrew Arnold, a medical oncologist, who has come from St. John's, Newfoundland, is based at the St. Joseph's Hospital Clinic. Dr. Mark Levine, who has transferred from St. Joseph's Clinic to the Henderson Clinic, has become Head of our Clinical Trials Department; he will expand the clinical research program. Dr. Michael Patterson, who has joined us as a radiation physicist, will supervise the commissioning of the new Therac 25 linear accelerator, which will be in operation in March 1985.

An outreach clinic is now active at Cambridge Memorial Hospital under the direction of Dr. James Gowing. At Joseph Brant Memorial Hospital in Burlington, an outreach clinic has also started under the steady hand of Dr. Peter McCulloch; eventually this will be co-ordinated by Dr. Alan Neville. The outreach clinic at McMaster University continues under the co-ordination of Dr. Peter McCulloch. The Niagara District Health Council has endorsed the concept of graded levels of cancer-care facilities to provide optimum care for patients in the Niagara Peninsula and has designated the Hamilton Regional Cancer Centre as the tertiary (level III) facility. A level II facility will be developed in St. Catharines and a level I or II facility in Niagara Falls. These outreach clinics, which are an integral part of the Hamilton Regional Cancer Centre, make possible the interaction of oncologists in private and in full-time academic practice to provide optimal care close to the patient's home.

The psychosocial support program for the cancer centre continues to expand under the direction of Drs. Bernie Trossman and Elizabeth Latimer; the latter has become co-ordinator of the regional palliative care program.

The new Hamilton Lodge at the Henderson Clinic is now in the advanced stages of construction.

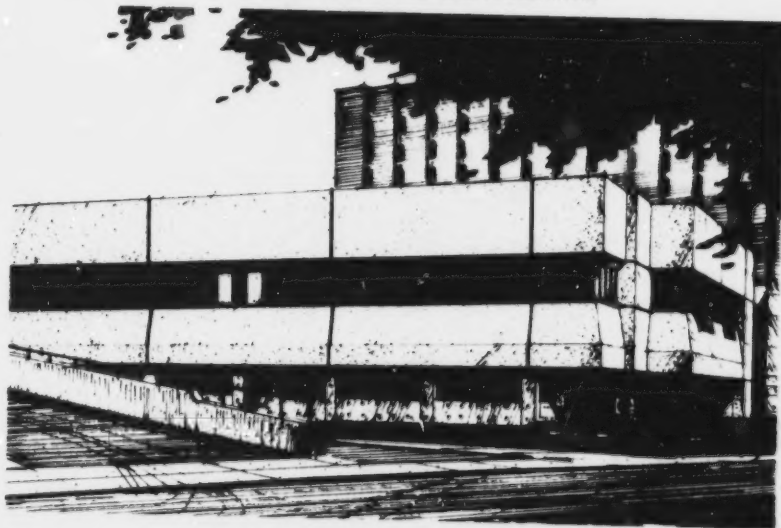
The CT scanner and the three-dimensional gamma camera in the radiology department of the Henderson Hospital have increased greatly our ability to determine extent of disease, volume of tumor and healing of bony lesions.

The 6 MeV linear accelerator has been reconditioned and the new 25 MeV linear accelerator is completing its acceptance trials.

A Cancer Information Service will be established as a pilot project by the Hamilton Regional Cancer Centre. The project represents a collaborative effort between the Ontario Cancer Treatment and Research Foundation and the Canadian Cancer Society Ontario Division. The target date for opening of this phone-in service is February 1, 1985.

A major emphasis at the Hamilton Regional Cancer Centre continues to be research into improving the results of treatment. This centre now has 1029 patients on local trials and 484 patients on national trials. A separate section, on page 118 describes these studies.

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Business Manager:

D. Steacy, B.Sc.

Senior Nurse and Radiotherapy Technician:

E. M. Bolster, Reg.N., R.T.

Social Service Nurses:

R. Crafts, Reg.N.

C. Keith, Reg.N.

Head of Medical Records:

R. S. Walker

Lodge Supervisor:

N. G. Ambury

Generally in Kingston 1984 was a productive year during which many projects were undertaken and several reached completion. The programs in the Medical Physics Division include continuation of the development of improved algorithms for electron-dose optimization, the development of an 81-detector matrix dosimeter for measuring beam uniformity, and the development of a fluorescence bronchoscope for the detection of early lung cancer.

Clinical studies included a review of endometrial carcinoma for the June 1984 Canadian Association of Radiologists (CAR) meeting, a review of radiotherapeutic techniques for the treatment of locally-excised breast cancer, the assessment of electrocautery in the management of pre-malignant lesions of the cervix, and an epidemiological and clinical review of cervix cancer in women under 35 (Gynecologic/Oncologic Division).

We continue to collaborate with the OCI in a study of the treatment of advanced epidermoid cancer at various sites with combined radiation and infusional chemotherapy. Also we continue to participate in the Clinical Trials Program of the NCIC, which is centred in Kingston under Dr. J. Pater's directorship. As Chairman of the CAR Advisory Council in Radiation Oncology, Dr. P. Froud continues his panCanadian surveys looking at manpower, equipment, and training programs.

Kingston's oncologists continue to devote a significant portion of their time and energy to education work, and Queen's University undergraduates and graduates have responded with a renewed interest in a career in oncology. The strong Ivan Smith Summer Studentship program, which has been maintained in Kingston, also makes a significant contribution to this welcome development. The visiting speakers brought to Kingston through the regular Thursday lecture series continue to broaden our experience, and strengthen the graduate and undergraduate training program.

P. J. Froud, M.B., Ch.B., D.M.R.T., F.F.R., F.R.C.P.(C)
Senior Radiation Oncologist

**LONDON REGIONAL CANCER CENTRE****VICTORIA HOSPITAL****Director:**

H. Bush, M.B., B.S., Ph.D.

Radiation Oncologists:

W. E. C. Allt, M.D.
P. Banerjee, M.B., B.S.
A. Cheung, M.D.
A. R. Dar, M.B., B.S.
J. A. Gilchrist, M.B., B.S.
J. A. Hammond, M.D.

Medical Oncologists:

V. Bramwell, M.B., B.S.
G. Cairncross, M.D.
W. I. Kocha, M.D.
L. Levin, M.B., Ch.B.
R. C. Lohmann, M.D.
D. Macdonald, M.D.
J. Skillings, M.D.

Physicists:

D. J. Dawson, Ph.D.
M. Gribble, M.Sc.
J. C. F. MacDonald, Ph.D.

Career Scientists:

A. Chambers, Ph.D.
J. Harris, Ph.D.
W. R. Inch, Ph.D.
D. J. Koropatnik, Ph.D.

Terry Fox Fellows:

J. D. Awde, D.D.S.
G. Bondy, M.D.
J. Gardner, Ph.D.

Administrator:

M. J. Morrison, M.P.A.

Business Manager:

E. Micallef

Nursing Co-ordinator:

M. J. Hodsman, B.Sc.N.

Senior Radiotherapy**Technologist:**

U. Ardy, R.T.T.

Social Worker:

A. Sawarna, M.S.W.

Head of Medical Records:

D. G. E. Ross, C.C.H.R.A.

Lodge Supervisor:

J. Stewart, Reg.N.

The past year again has seen physical and conceptual changes in the further evolution of the London Regional Cancer Centre. Extensions to the Centre have included a new chemotherapy suite and a new clinical word-processing area. The latter has allowed the new head of medical records, Don Ross, to restructure the secretarial services and introduce new concepts in organizing medical records. The chemotherapy suite provides a focal point for practical training of chemotherapy nurses and the nursing department is helping to train chemotherapy nurses from peripheral clinic hospitals and student nurses from the University of Western Ontario training program.

Psychosocial services have expanded rapidly, and with the recruitment of two new social workers — Shelly Markland and Betty Stewart, this service has become a major activity. In tandem with this development, a palliative care team has been set up and is co-ordinated by Dr. Robin Shearer with active support from Dr. Jackie Gardner. This team co-ordinates outpatient palliative care for patients registered with the Centre and is represented by community-based nursing services, family physicians, oncologists, clinical and hospital nurses, and social workers.

With the addition of another clinical trials nurse, Wendy Gillis, the clinical trials unit has expanded to meet the increasing demand for this important facility. Dr. Vivian Bramwell, a medical oncologist from Manchester, joined us last year and we welcome her expertise especially in Phase I clinical study. The development of a successful gynecology tumor board and a GU tumor study group emphasizes further our multidisciplinary approach to cancer treatment, research and education. A viable pulmonary oncology group has been established and a hematology/lymphoma study group will hold its first meeting in the Fall. Accrual to the breast screening program is now complete.

The opening of a dental room in the Centre, has prepared the groundwork for the introduction of dental oncology. Dr. Doug Awde, who joined us this year as a Terry Fox Fellow, likely will lead in the development of dental oncology once his research commitment is complete. Experimental oncology continues to expand its horizons. The Terry Fox laboratories were opened this year and, with four career scientists and three Terry Fox Fellows well into their research programs, basic biological cancer research has become an integral part of the Centre's program.

The District Health Council has approved the functional program for the new clinic and we hope that the initial planning will begin soon. A computerized scheduling

system now in place represents the first phase of a more comprehensive computerization facility in the Centre.

It is with great pleasure that we welcome our new administrator, Mary Jean Morrison. We wish her every success. Mary Jean succeeds Christine Harman, whose energy and initiative were responsible for many improvements in the Centre's operation.

Leslie Levin, M.B., Ch.B., M.D., M.R.C.P., F.R.C.P.(C)
Senior Medical Oncologist

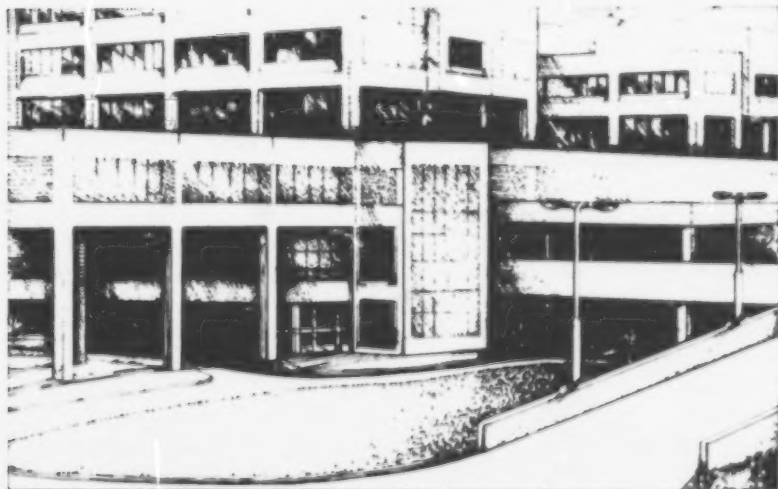


OTTAWA REGIONAL CANCER CENTRE

**OTTAWA CIVIC HOSPITAL
OTTAWA GENERAL HOSPITAL**



AND OTTAWA GENERAL HOSPITAL



Director:

G. E. Catton, M.B., B.S.

Career Scientist:

H. C. Birnboim, M.D.

Radiation Oncologists:

C. J. E. Danjoux, M.D.

L. Eapen, M.D.

P. Genest, M.D.

A. L. Girard, M.D.

R. S. R. McDermot, M.D.

B. D. Nair, M.B., B.S.

Physicists:

L. H. Gerig, B.Sc.

P. M. Pfalzner, M.Sc.

Business Manager:

S. McAdam

Medical Oncologists:

C. Cripps, M.D.

W. E. Hirte, M.D.

J. A. Maroun, M.D.

D. J. Perrault, M.D.

D. J. Stewart, M.D.

V. P. J. Young, M.D.

Nurse Administrator:

C. J. MacMillan, B.Sc.N.

Head Nurse (General Hospital Division):

L. Fawcett, R.N.

Clinical Assistants:

K. R. Hopkinson, M.D.

N. Pearce, M.D.

I. A. Prosser, M.D.

B. V. Reddy, M.D.

S. J. Wong, M.D.

Lodge Supervisor:

J. M. Davidson, Reg.N.

Senior Radiotherapy Technician:

R. P. Wallace, A.C.T.

Heads of Medical Records:

M. C. Therrien (Civic Hospital Division)

M. M. Brassard (General Hospital Division)

During the past year, Drs. Paul Genest and Bhavani Nair have joined the Centre as radiation oncologists; Dr. Hyman C. Birnboim as Head of Experimental Oncology and Mr. Bruce Faddegon as Physicist-in-training.

On June 30, 1984, Dr. J. T. Nichol retired after 14 years service as a radiation oncologist.

In July 1984, Dr. Leo L. Stolbach, who was Chief of Medical Oncology, elected to return to Boston to pursue psychosocial research.

In November 1983, Dr. Jean Maroun co-ordinated a one day refresher course in oncology on "Curable Cancer". It was held in conjunction with the University of Ottawa and the Continuing Medical Education Department of the Ottawa General Hospital. Guest speakers were Dr. R. Margolese from Montreal and Dr. Cornelia Baines from Toronto.

On October 14, 1983, at a graduation ceremony, Lisa Belanger and Roberta Yeldon became qualified radiation technologists and both remain on staff.

Integration of computer facilities within the Centre is progressing. Patient enrolment, case registration data and appointment scheduling are now all functional.

On September 25 and 26, 1984, Dr. Philip Rubin, Professor of Radiation Oncology at University of Rochester, was at the Centre as the Vail Visiting Professor. His major address was entitled "Hodgkin's Disease: Is There a Price for Successful Treatment?".

On October 1 and 2, 1984, the first Hyperthermia Workshop, organized by the Ottawa Regional Hyperthermia Group, was held in Ottawa. This group came into being through the joint efforts of five local organizations: the Ottawa Regional Cancer Centre, Atomic Energy of Canada Limited, the National Research Council of Canada, and the two Universities in Ottawa. Additional financial help for this workshop was provided by Bristol Pharmaceutical Company, the BSD Medical Corporation, Clini-Therm, Macom Incorporated, Tag-Med and Uri Therm-X Incorporated to support a total of twelve invited speakers. The total registration was 85.

G.E. Catton, M.B., B.S., D.M.R.T., F.R.C.P.(C)
Director

**THUNDER BAY REGIONAL CANCER CENTRE****GENERAL HOSPITAL OF PORT ARTHUR****Director:**

J. F. Kotalik, M.D.

Business Manager:

M. M. Ryan

Radiation Oncologists:

W. A. Hargan, M.D.

F. H. W. Hellmuth, M.D.

Senior Nurse:

L. Bright, R.C.N.

Medical Oncologist:

M. D. E. Goodyear, M.B.B.S.

Supervisory Radiotherapy Technician:

J. V. Morgan, R.T.

Clinical Assistant:

J. A. Chalykoff, M.D.

Nurse Social Worker:

V. Coley, R.C.N.

Physicist:

P. D. Sharma, M.Sc.

Head of Medical Records:

M. P. Winfield, C.C.H.R.A.(A)

Lodge Supervisor:

B. C. Petty

1984 has been a year of internal consolidation and development of increased external contacts. To accommodate the increased number of chemotherapy patients and the use of multiple drugs and prolonged infusions, our operating room was converted into a day-care unit, with the financial assistance from a former patient. The number of patients entering clinical trials, which has increased markedly, will continue to grow further because we have become members of North Central Cancer Treatment Group, which is led by the Mayo Clinic. This relationship is important because the Mayo Clinic continues to serve as a tertiary referral centre for Northwestern Ontario. We have further developed our program of continuous medical education for the local medical community by introducing a program of "clinical trial" dinners. These meetings allow us to discuss current treatment policies for various tumor sites, new drugs and pertinent clinical trials at a forum attended by most of the city's physicians. We have begun to implement the concept of primary nursing in our Centre with particular stress on psychosocial support and symptoms management. A workshop program is underway to teach pain control to nurses of our host hospital.

This year, two radiotherapy technologists graduated from our training program and one new student was admitted into this program. We enjoyed having with us an Ivan Smith summer student — Mr. Heman Chow, a medical student from University of Toronto.

Difficulties encountered in delivering medical oncology care on the periphery of our large region led us to propose an outreach program for Fort Frances and area. Training of staff for this program is underway.

An agreement was reached on affiliation between our centre and McMaster University in Hamilton. This will provide necessary academic contacts and stimulation for our staff and will facilitate our teaching and research activities.

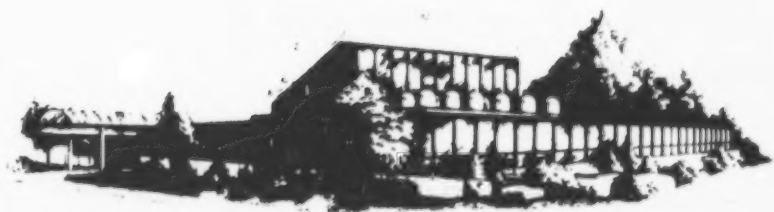
After serving the centre for almost 20 years and becoming a friend to many of our staff and patients, Mrs. Edie Taylor has retired to pursue her many other interests. She was replaced as Executive Secretary by Mrs. Loretta Russell.

Over this last year, the expansion of our service activities and the introduction of certain new programs was possible only because all our staff made a considerable effort to compensate for the absence of two physicians. All are looking forward to early additions to our medical staff.

J. F. Kotalik, MD, DMRT, FRCPC
Director



TORONTO-BAYVIEW REGIONAL CANCER CENTRE
SUNNYBROOK MEDICAL CENTRE



Director:

R. D. T. Jenkin, M.B.B.S.

Radiation Oncologists:

M. P. Berry, M.B.B.S.
P. A. Catton, M.D.
R. G. MacKenzie, M.D.
I. Ackerman, M.D.

Medical Oncologists:

N. Iscoe, M.D.
I. J. Kerr, M.D.
D. Osoba, M.D.
J. J. Rusthoven, M.D.
D. J. A. Sutherland, M.D.

Clinical Assistants:

H. M. Kocandrie, M.D.
T. B. McQuiston, M.D.
I. Chang, M.D.

Physicists:

H. B. Michaels, Ph.D.
P. F. O'Brien, M.Sc.
R. A. Siwek, Ph.D.

Administrator:

L. D. Langdon, M.H.A.
(to October 19, 1984)
H. B. Wodinsky, M.H.Sc.
(from January 1, 1985)

Senior Nurse:

C. Johnston, Reg.N.

Senior Radiotherapy Technician:

A. Bissett, R.T.(T)

Head of Medical Records:

M. Mistruzzi, C.C.H.R.A.(C)

Once again 1984 was a year of growth for the Toronto-Bayview Regional Cancer Centre. The estimated number of new patients registered for the year is 2100 and, by year's end, the rate of new patient registration will approximate 2500/year. Growth was particularly marked in the Department of Radiation Oncology. The 25 MeV linear accelerator came on line early in the year. Our second 25 MeV accelerator is scheduled for delivery in February 1985. The number of patients who attended daily for radiation treatment increased from 40 to 50 in December 1983 to 70 to 80 in December 1984. Now over 3000 patients visit the Centre each month for all purposes. This increase is reflected in the increased number of employees, now 100 compared to 78 one year earlier, an increase of 28%. Dr. Ida Ackerman joined the full-time staff as radiation oncologist and Dr. Iris Chang was appointed as a clinical assistant.

In October, we were the host centre for the Foundation's 23rd Clinical Conference, which was held at the Inn on the Park, Toronto; it attracted 215 registrants. Speakers from the OCTRF, and the OCI and a number of invited guests from the United States and overseas reviewed the treatment of localized Hodgkin's disease and non-Hodgkin's lymphoma. All hope that this review will assist the formulation of improved treatment policies within the province.

In May, Toronto was host to the Annual Meeting of the American Society of Clinical Oncology. Dr. David Osoba was responsible for the local arrangements for this large successful meeting.

During the year, a Metropolitan Toronto "users committee" was set up to examine the organization of and the needs for radiation oncology within this geographic area, which is served by two centres. The principal objectives of the committee are improved use of equipment and increased professional collaboration. As an example of such collaboration between the centres, we would note that the second 25 MeV accelerator being installed at the Toronto-Bayview Centre will be used by the Princess Margaret Hospital staff during the period when the old Betatron is being removed and the new high-energy accelerator is installed at that centre. As soon as this second high-energy accelerator comes into operation, more than 100 patients a day will be irradiated at the Toronto-Bayview Centre.

We regret to report that in October our first administrator, Lorne Langdon, resigned. The major contributions which Lorne made to the growth and current health of this Centre were cited during the farewell "events" to mark his departure.

R. D. T. Jenkin, M.D., B.S., F.R.C.R., F.R.C.P.(C)
Director



**WINDSOR REGIONAL CANCER CENTRE
METROPOLITAN GENERAL HOSPITAL**



Acting Director:

G. C. K. Mok, M.D.

Business Manager:

E. Schwindt

Radiation Oncologist:

J. H. Maus, M.D.

Senior Radiotherapy Technician:

R. Macpherson, R.T.

Medical Oncologists:

H. T. Abu-Zahra, M.B., B.Ch.

D. B. McDonald, M.D.

S. Yoshida, M.D.

Senior Nurses:

A. Beaton, Reg. N.

M. O'Neill, Reg. N.

Physicist:

D. Smocovitis, M.Sc.

Head of Medical Records:

V. L. Gignac

During 1984, the Windsor Regional Cancer Centre continued its service to the citizens of Essex County and adjoining area, without any substantial change in new patient intake. There have been some staff changes during the year. Dr. T. A. Watson, former Director of the London Regional Cancer Centre, has been of great assistance on a sessional basis two days a week during a busy spring and summer period. Dr. Maus, former Director of the Windsor Centre, had been called out of town for many meetings of the Role Study Committee and of the clinic directors, and Dr. Watson has bridged the gap to maintain service to patients.

Dr. Margaret J. Foote, a general practitioner and a former resident of the Brantford area, has moved to Windsor with her husband, an Anglican priest, who is in charge of one of our churches. Margaret is serving as a clinical assistant in the Radiation Oncology Division. She brings to us six years' experience in general practice and comes well recommended by her confreres in Brantford. We welcome her to the Radiation Therapy Division.

During 1983 and 1984 a Search Committee was struck to find a new Director, in view of the retirement of Dr. J. H. Maus who has been the Director since 1963. Dr. G. C. K. Mok, who has been with the Foundation since 1959 as a radiation oncologist, was appointed Acting Director effective July 1, 1984. We welcome him to his new appointment. We have been unsuccessful in attracting a second radiation oncologist to Windsor and Dr. Maus will continue in that capacity until the end of 1984.

The Medical Oncology Division continues to carry a heavy workload embracing the outpatient service in Metropolitan Hospital and inpatient services in four general hospitals of Windsor and, to a certain extent, the Leamington General Hospital. Also at the Leamington District Hospital a busy peripheral clinic operates on Thursday mornings to provide outpatient services, primarily chemotherapy.

Our staff continues to follow the protocols of the National Cancer Institute of Canada and the Southwest Oncology Group. Also, in the near future, we hope to enter cases into the Ontario Clinical Oncology Group's first protocol study of the treatment of limited cancer of the breast.

In Windsor, as in every other centre, financial constraints have tended to restrict the employment of new staff. On several occasions "doubling up" has been necessary because six of our staff members have taken maternity leaves at various times throughout the year.

With regard to patient registration for information systems, university students have helped with our backlog in the entry of previous case material. We acknowledge with gratitude the assistance of volunteers of the Canadian Cancer Society Ontario Division and the Essex County District in particular, and the Hospice of Windsor. They have been of great benefit to our patients, helping the patient and family to adjust to the discovery of cancer.

J. H. Maus, M.D.
Radiation Oncologist

SERVICE LOAD

The following five tables describe the service load of the Foundation's seven regional cancer centres during the calendar year 1983. As of January 1, 1982, with the implementation of the Patient Care Management System in the cancer centres, it has been possible to retrieve data in more detail than was possible in previous years. However, the system has not been implemented completely and hence the tabulations are marked "provisional". It must be emphasized that these tables are comparable only with the service load tables published for 1982, and not for those for the years before this. Also, they are not comparable with the data for the fiscal year presented for the Princess Margaret Hospital.

In 1983, 40,633 patients were seen at the Foundation's regional cancer centres. Of these, 93% had malignant lesions and, of these lesions, 11,432 were new to the centres (Table I). Of cases referred for non-malignant conditions, 88% were first seen in 1983 (Table II). The majority of these, 1499, were seen in consultation. In all, 11,405 cancer cases were treated by radiotherapy (Table III); of these 5484 were treated by cobalt units, 3779 by a linear accelerator, and 2142 by other methods of radiotherapy.

During the year, patients made 373,329 visits to the regional cancer centres and the majority, 117,867 were for treatment of malignant disease (Table IV). Of these treatments, 70% were given on an outpatient basis (Table V).

TABLE 1*
Malignant Caseload During 1983¹

TREATMENT CENTRE	TREATED			SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL	
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy			Other
Cases New in Current Year						
Hamilton	1,084	138	346	69	959	2,596
Kingston	487	111	119	42	418	1,177
London	1,042	184	199	143	830	2,398
Ottawa	884	169	363	150	903	2,469
Thunder Bay	182	30	51	—	180	443
Toronto-Bayview	470	128	100	195	507	1,400
Windsor	319	59	186	9	376	949
TOTAL	4,468	819	1,364	608	4,173	11,432
Cases Registered in any Previous Year						
Hamilton	427	158	752	25	4,072	5,434
Kingston	197	86	222	86	2,294	2,885
London	324	162	416	206	5,190	6,298
Ottawa	353	264	785	163	5,354	6,919
Thunder Bay	67	39	137	1	961	1,205
Toronto-Bayview	78	66	131	30	637	942
Windsor	79	63	394	5	2,203	2,744
TOTAL	1,525	838	2,837	516	20,711	26,427
TOTAL ALL MALIGNANT	5,993	1,657	4,201	1,124	24,884	37,859

* Provisional (transition period — see text)

¹ Includes cases seen at peripheral clinics.

TABLE II*
Other (Non-Malignant) Caseload During 1983¹

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
Cases New in Current Year						
Hamilton	40	—	33	17	275	365
Kingston	16	4	17	35	236	308
London	78	—	129	268	448	923
Ottawa	9	—	2	85	133	229
Thunder Bay	11	1	—	1	54	67
Toronto-Bayview	6	1	4	189	187	387
Windsor	14	—	14	—	166	194
TOTAL	174	6	199	595	1,499	2,473
Cases Registered in any Previous Year						
Hamilton	2	—	4	—	19	25
Kingston	1	—	4	4	51	60
London	2	—	9	18	69	98
Ottawa	1	—	1	2	14	18
Thunder Bay	1	1	1	—	6	9
Toronto-Bayview	1	—	2	16	57	76
Windsor	—	—	2	—	43	45
TOTAL	8	1	23	40	259	331
TOTAL OTHER	182	7	222	635	1,758	2,804

Provisional (transition post-4

* Provisional (transition period — see text)

¹ Includes cases seen at peripheral clinics.

TABLE III*
Cases Treated During 1983 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
				Malignant Neoplasms				
Superficial x-ray	330	204	123	36	36	36	—	765
Deep x-ray	87	63	—	—	21	4	129	304
Cobalt ⁶⁰	1,477	576	638	1,228	369	648	548	5,484
Cesium ¹³⁷	—	1	2	—	3	—	—	6
Betatron	—	—	495	—	—	2	—	497
Linear accelerator	570	461	1,207	1,161	—	380	—	3,779
Intracavitary	133	33	99	64	15	—	47	391
Interstitial	—	9	47	5	2	1	1	65
Moulds and applicators	—	—	13	99	—	—	—	112
Systemic isotopes	—	—	—	—	—	—	—	—
Others	—	—	2	—	—	—	—	2
SUB-TOTAL	2,597	1,347	2,626	2,593	446	1,071	725	11,405
				Other Non-Malignant				
Superficial x-ray	23	6	36	—	9	—	—	74
Deep x-ray	—	2	—	—	—	—	13	15
Cobalt ⁶⁰	18	5	14	8	11	5	2	63
Cesium ¹³⁷	—	—	—	—	—	—	—	—
Betatron	—	—	1	—	—	—	—	1
Linear accelerator	6	7	19	2	—	4	—	38
Intracavitary	—	4	—	—	—	—	—	4
Interstitial	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	—	—	—	—	—	—
Systemic isotopes	—	—	—	—	—	—	—	—
Others	—	—	10	—	—	—	—	10
SUB-TOTAL	47	24	80	10	20	9	15	205
TOTAL [†]	2,644	1,371	2,706	2,603	466	1,080	740	11,610

* Provisional (transition period — see text)

† A case can be treated by more than one method per year.

TABLE IV*
Service Load, 1983

TREATMENT CENTRE	VISITS FOR					TOTAL VISITS
	Treatment		Other	Non-Treatment		
	Radiation	Chemotherapy Immunotherapy		Simulation	Consultation or Follow-up	
	Visits for Malignant Neoplasms					
Hamilton	24,812	9,013	849	3,076	31,921	69,671
Kingston	12,955	2,689	846	1,480	16,492	34,462
London	28,288	4,928	1,301	3,389	36,081	73,987
Ottawa	26,731	11,587	1,519	2,346	50,272	92,455
Thunder Bay	5,310	1,404	82	320	6,874	13,990
Toronto-Bayview	9,479	2,725	602	1,065	19,979	33,850
Windsor	10,292	6,660	441	904	28,409	46,706
TOTAL	117,867	39,006	5,640	12,580	190,028	365,121
	Other Non-Malignant					
Hamilton	314	189	122	53	903	1,581
Kingston	152	32	106	26	528	844
London	514	179	735	90	1,405	2,923
Ottawa	116	13	293	9	322	753
Thunder Bay	138	13	2	9	176	338
Toronto-Bayview	166	11	235	11	712	1,135
Windsor	131	27	61	19	396	634
TOTAL	1,531	464	1,554	217	4,442	8,208
TOTAL ALL VISITS	119,398	39,470	7,194	12,797	194,470	373,329

*Provisional (transition period — see text)

TABLE V*
Treatments by Radiation During 1983, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO BAYVIEW		WINDSOR		TOTAL	
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
	Malignant Neoplasms															
Superficial x-ray	27	1,634	32	801	12	545	—	178	—	183	5	166	—	—	76	3,507
Deep x-ray	54	265	15	306	—	—	—	—	11	97	—	35	27	1,423	107	2,126
Cobalt ⁶⁰	2,900	12,192	1,726	4,768	1,685	7,123	2,575	10,896	912	4,327	1,339	4,392	1,629	7,738	12,766	51,436
Cesium ¹³⁷	—	—	71	—	121	—	—	—	131	—	—	—	—	—	323	—
Betatron	—	—	—	—	501	5,309	—	—	—	—	—	42	—	—	501	5,351
Linear accelerator	894	7,776	762	5,331	3,984	8,441	1,685	12,151	—	—	731	3,830	—	—	8,056	37,529
Intracavitary	133	—	33	—	99	—	64	—	15	—	—	—	47	—	391	—
Interstitial	—	—	8	—	33	14	5	—	2	—	1	—	1	—	50	14
Moulds and applicators	—	—	—	—	—	13	2	97	—	—	—	—	—	—	2	110
Systemic isotopes	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Others	—	—	—	—	—	8	—	—	—	—	—	—	—	—	—	8
SUB-TOTAL	4,008	21,867	2,647	11,206	6,435	21,453	4,331	23,322	1,071	4,607	2,076	8,465	1,704	9,161	22,272	100,081
METHOD OF TREATMENT	Other Non-Malignant															
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
	Other Non-Malignant															
Superficial x-ray	—	46	—	26	—	36	—	—	—	28	—	—	—	67	—	136
Deep x-ray	57	76	9	6	41	68	37	47	45	65	8	30	—	58	197	74
Cobalt ⁶⁰	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	350
Cesium ¹³⁷	—	—	—	—	—	20	—	—	—	—	—	—	—	—	20	—
Betatron	3	129	—	104	83	216	—	15	—	—	5	103	—	—	91	567
Linear accelerator	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4	—
Intracavitary	—	—	4	—	—	—	—	—	—	—	—	—	—	—	—	—
Interstitial	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Moulds and applicators	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Systemic isotopes	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Others	—	—	—	—	—	38	—	—	—	—	—	—	—	—	—	36
SUB-TOTAL	60	251	13	143	124	378	37	62	45	93	13	133	—	125	292	1,185
TOTAL OF ALL TREATMENTS	4,068	22,118	2,660	11,349	6,559	21,831	4,368	23,384	1,116	4,700	2,089	8,598	1,704	9,286	22,564	101,266

* Provisional (transition period — see text)

ONTARIO CANCER INSTITUTE

incorporating

PRINCESS MARGARET HOSPITAL

Director:

R. S. Bush, M.D.

Medical Oncology
(Clinical and Research):

R. E. Alison, M.D.
D. E. Bergsagel, M.D.
N. F. Boyd, M.B. B.S.
R. Corringham, M.B. B.S.
J. E. Curtis, M.D.
C. Erlichman, M.D.
R. Feld, M.D.
S. Fine, M.D.
R. Hasselback, M.D. C.M.
H. A. Messner, M.D.
M. D. Minden, M.D.
I. C. Quirt, M.D.
J. F. G. Sturgeon, M.B. B.S.
I. F. Tannock, M.D.
D. Warr, M.D.

Radiation Oncology
(Clinical and Research):

F. A. Beale, M.B. Ch.B.
H. A. Bean, M.D.
R. M. Clark, M.B. B.S.
B. J. Cummings, M.B. Ch.B.
A. J. Dembo, M.B. Ch.B.
P. J. Fitzpatrick, M.B. B.S.
M. K. Gospodarowicz, M.D.
M. A. Gribbin, M.B. B.S.
A. R. Harwood, M.B. Ch.B.
N. V. Hawkins, M.B. B.S.
T. J. Keane, M.B. Ch.B.
D. G. Payne, M.D.
J. F. Pringle, M.B. Ch.B.
G. A. Rawlings, M.D.
W. D. Rider, M.B. Ch.B.
W. J. Simpson, M.D.
S. B. Sutcliffe, M.D.
G. M. Thomas, M.D.
J. L. Yeoh, M.D.

Diagnostic Radiology:

R. Blend, M.B. B.S.
S. Herajan, M.D.
I. F. Majesky, M.D.
P. Y. Poon, M.B. B.S.
D. F. Rideout, M.B. B.S.

Nuclear Medicine:

G. N. Ege, M.D.

Pathology:

C. Bergeron, M.D.
T. C. Brown, M.D.
J. S. Carruthers, M.D.
V. L. Fornasier, M.D.
G. J. Laroye, M.D.
B. J. Patterson, M.D.
M. E. Platts, M.D.
L. M. Sugar, M.D.
T. Treger, M.D.

Microbiology:

P. G. Tuffnell, M.D.

Physics (Clinical and Research):

M. C. Archer, Ph.D.
M. J. Bronskill, Ph.D.
J. R. Cunningham, Ph.D.
A. Fenster, Ph.D.
S. Foster, Ph.D.
D. M. Galbraith, B.Sc.
M. Henkelman, Ph.D.
R. P. Hill, Ph.D.
J. W. Hunt, Ph.D.
B. Japp, B.Sc.
P. M. K. Leung, Ph.D.
H. Maharaj, B.Sc.
A. Monari, M.Sc.
P. N. Munro, M.Sc.
F. P. Ottensmeyer, Ph.D.
A. M. Rauth, Ph.D.
A. J. Rawlinson, M.Sc.
W. B. Taylor, B.Eng.
J. Van Dyk, M.Sc.
H. P. Webb, C.E.T.
G. F. Whitmore, Ph.D.
M. Yaffe, Ph.D.

Biological Research:

S. Benchimol, Ph.D.
 A. Bernstein, Ph.D.
 R. Buick, Ph.D.
 A. Ciampi, Ph.D.
 A. J. Cunningham, Ph.D.
 R. M. Gorczynski, Ph.D.
 N. Hozumi, Ph.D.
 V. Ling, Ph.D.
 T. W. Mak, Ph.D.
 E. A. McCulloch, M.D.
 R. G. Miller, Ph.D.
 R. A. Phillips, Ph.D.
 J. E. Till, Ph.D.

Biostatistics:

G. DeBoer, Ph.D.
 D. Tritchler, Ph.D.

Administrator:

J. E. Ratz

Assistant Administrators:

E. Govoni
 J. P. Holder, Reg.N.
 T. J. D. West
 W. Wilkinson

Head of Medical Records:

A. Buchanan, B.A., C.C.H.R.A.(C)

Librarian:

C. Morrison, B.A., M.L.S.

The Hospital and Institute, having celebrated Silver Anniversaries, now look ahead to a new era in scientific and clinical research and patient care. The staff have a golden opportunity to learn more about the nature of cancer and to build upon the efforts and success of the first 25 years. To mark its first phase, a Quarter-Century Club was established when the Hon. John Aird, Lieutenant Governor of Ontario, joined members of the OCI Board at a luncheon in honor of the staff members and volunteers who have been with the Institute since 1958. The 43 founding members include 14 volunteers and 29 staff members.

In June an Open House organized around the theme "25 Years of Care and Research" was held to illustrate the OCI's multidisciplinary approach to treatment and its commitment to excellence in patient care. This was preceded by an OCI/PMH Fun Run, which attracted 180 registrants, who walked or ran over 2 km. At the Open House Mayor Eggleton brought greetings from the City of Toronto. A reception held in the Lodge honored 45 patients who had been treated at PMH. The Lodge and Hospital had numerous exhibits to provide an historical overview and to describe recent advances in research and patient service.

The year, which was dominated by internal and external assessments and planning, saw the initiation of a new Provincial Role Study. In 1973, recommendations made in a similar study led to the development of the west wing with an increased number of beds and improved outpatient facilities. Regrettably the second phase, which would have provided new outpatient facilities and a modern radiotherapy department, was shelved because the Ministry of Health could not commit sufficient funding. This setback has increased greatly the difficulty in meeting the increased demands for care and, as a result, some of those needing radiotherapy have to wait because the facilities and staff are overstretched and the equipment is aging. The

problems are compounded. We must obtain new equipment and resources at once if the Princess Margaret Hospital is to maintain its position as a world leader in radiation oncology. In this respect our staff cannot explore the international trend to multiple daily fractions of radiation because of the shortage of facilities. In addition there is evidence that some tumors respond better to higher doses of radiation given in longer periods than is customary at PMH. The current waiting list prevents us from doing similar studies.

In 1983 the number of new patients was similar to that in the previous year. Altogether, between April 1983 and March 1984, the staff saw 7534 new cases of which 6997 were malignant. The spectrum of tumors remains unchanged; the most common are those of lung and breast, with more than 1100 of each. In recent years there has been a steady decline in the number of patients with skin cancer other than melanoma. This change reflects better patient education, and earlier diagnosis and treatment by other methods. In patients under 17 we saw 148 tumors; the most common of these were leukemia, medulloblastoma, neuroblastoma and nephroblastoma.

The number of radiation treatments increased by 3% to 85,996. There was a small decrease in the use of cobalt radiation with a more than compensatory increase in the use of linear accelerators. We expect this trend to continue as units become available.

Although the hospital maintains standards of medical care, which exceed those required for accreditation by the Ontario Hospital Association, we have never sought to be accredited. Now it has been decided that the hospital should become accredited and all departments have been busy developing plans to achieve this goal in 1985. We expect to have a formal organization for the medical staff so that it can elect officers as recommended in the Public Hospitals Act. It is hoped that this formalization of the medical staff (a necessary requirement for accreditation) will strengthen the lines of communication between the hospital's executive committees and the OCI Board.

The hospital continues to support the peripheral clinic service which is an outreach program to patients and physicians living far from Toronto. Four clinics located in Northeastern Ontario accounted for over two-thirds of the 7000 patients seen at such clinics. In recent years these figures remain fixed because of limited resources, particularly of medical manpower. To maintain this service, the base hospital must do without the equivalent of one full-time staff member every working day. Recently, the Northeastern Role Study recommended the establishment in Sudbury of a fully staffed and equipped cancer centre within the next few years. As a prelude, the OCTRF has appointed a full-time medical oncologist to serve the Manitoulin-Sudbury area. Dr. R. Corringham now supervises the chemotherapy program at Laurentian Hospital in Sudbury and participates in the monthly clinics.

The reputation of the PMH/OCI can be measured by its academic record. Its staff delivered more than 350 lectures and papers outside of the institute and published over 150 papers. In addition, many of the staff have delivered named lectures and have served as a visiting professor to other universities. All departments

are involved in educational programs such as the national program for training radiation technologists and the extensive in-service programs for nurses. Drs. I. C. Quirt and S. Fine received awards for excellence in clinical teaching.

Clinical research continues through retrospective and prospective studies and numerous clinical trials, which are underway, involve all of the professional staff. Because thyroid cancer is uncommon, the Canadian Association of Radiologists is sponsoring a cross-Canada study to determine optimal treatment and prognostic factors. Between 1958 and 1973, this study located 2214 patients and these records are being examined to establish prognostic factors and optimal care. In-depth studies continue in malignant lymphoma and Hodgkin's disease, and in the use of chemotherapeutic agents as adjuvants to radiation in the treatment of carcinoma of the cervix and epithelial tumors of the head and neck. In carcinoma of the esophagus, it appears that mitomycin C and 5-fluorouracil used in combination with split-course radiotherapy significantly improves the two-year survival rate. Malignant melanoma is the most serious of the cutaneous cancers. The hospital has participated in several collaborative programs sponsored by the NCIC which employ chemotherapy and immunotherapy as adjuvants to primary treatment. The results are disappointing and no single approach shows any advantage. It has been shown that the development of melanoma is related to exposure to sunshine and so a new program has been implemented to promote prevention and encourage the use of sunscreens. Lung cancer remains the most common single cancer in both men and women, and these patients succumb to both local and metastatic disease. Several trials continue which combine aggressive chemotherapy with radiotherapy. The bone-marrow transplant program, which serves mainly patients with leukemia, has been expanded to a 12-bed unit with one patient being transplanted each week. A total of 120 transplants have been performed since 1970 with an overall survival of 50% with 60/120 patients alive at a median follow-up of 23 months.

When the NCIC made on-site visits to the research divisions of biology and physics, it found a firm research foundation in place and were able to endorse the efforts of staff members. Major projects in these divisions included the investigation of leukemia in the laboratory and clinic, and in association with the marrow transplant program. Cytotoxic T-lymphocytes play a major part in the capacity of the immune system to distinguish self from non-self. A major achievement of the OCI was the successful recognition and characterization of the gene that specifies that a cell will be a T-cell. This discovery opens the door to studies which will determine how the immune system operates both in relation to malignancies and in many other diseases. Radiosensitization in hypoxic cells was investigated by using small doses in multiple daily fractions and in association with chemotherapeutic agents used as adjuvants to radiation. The clinical physicists used computers to investigate the dosage patterns for the electron beam and irregularly shaped photon fields. CT images were used for detailed anatomic information. These studies were aimed at improving the physical and technical aspects of radiotherapy. Magnetic resonance imaging has been explored in 7600 patients and volunteers to assess the diagnostic accuracy of the technique

and to compare it with other imaging modalities. In particular, NMR has been used to study the spread of lung cancer within the chest.

Treatment of cancer can be exhausting for the patient. Optimal treatment requires control of the cancer with good survival and a reasonable quality of life. Studies have begun on the health status of treated patients with different cancer to determine the best regimens. Many physicians know that the mind-body relationships can influence chronic diseases including cancer. We are studying psychological support to determine whether a positive response from the patient can slow the progress of the tumors.

This year Dr. W. D. Rider, the head of radiation oncology, will retire after 28 years at the OCl. His original contributions, his savoir-faire and his drive have helped to establish this group as a world leader in clinical and radiation oncology.

The Annual Report contains further details of the work of the PMH/OCl.

P. J. Fitzpatrick, M.B., B.S.

Radiation Oncologist

TABLE VI*

Pediatric Cases Under 17 Years of Age Treated at PMH
April 1983 — March 1984

Leukemia	31
Lymphomas:	
Hodgkin's disease	4
Non-Hodgkin's lymphoma	2
Bone tumors:	
Osteosarcoma	1
Other	2
Sarcomas:	
Rhabdomyosarcoma	6
Other sarcomas	4
CNS:	
Medulloblastoma	10
Ependymoma	3
Astrocytoma	5
Other gliomata	5
Other CNS tumors	7
Neuroblastoma	15
Nephroblastoma	10
Retinoblastoma	5
Other malignant neoplasms	13
Benign and non-neoplastic lesions	25
TOTAL	148

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1983-1984.

TABLE VII*

**Number of Treatments Given
in the PMH Department of Radiotherapy
April 1983 — March 1984**

EXTERNAL BEAM	
Superficial x-ray	1,670
Deep x-ray	3,574
Cobalt	43,417
Linear accelerators:	
Low energy	6,376
High energy	25,933
Betatron	5,026
TOTAL	85,996
Inpatient treatments	17,419
Outpatient treatments	68,577
TOTAL	85,996
SEALED SOURCES	
Intracavitary	290
Interstitial (needles, wires and seeds)	33
Strontium applicators	122
TOTAL	445

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1983-1984.

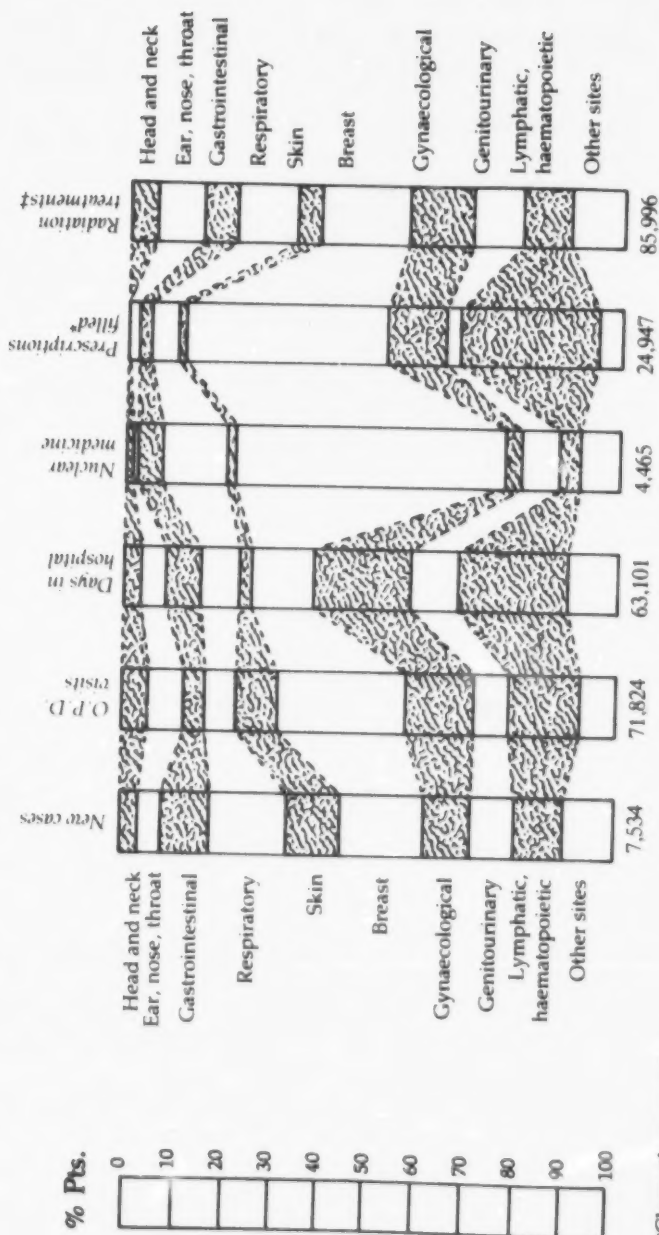
TABLE VIII*

**Services Provided by PMH at Peripheral Clinics
April 1983 — March 1984**

CLINIC	NEW PATIENTS SEEN		PERIPHERAL CLINIC VISITS**	
	Malignant	Other	Malignant	Other
North Bay	125	10	1,291	48
Owen Sound	71	4	713	19
Peterborough	39	2	1,765	32
Sault Ste. Marie	65	3	785	19
Sudbury	23	1	1,204	16
Timmins	41	11	1,012	39
TOTAL	364	31	6,770	173

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1983-1984.

**Including the visits when patients are first seen at peripheral clinics as well as subsequent visits for new and old patients.



*Chemotherapy only

†External beam only

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Fig. 1. Princess Margaret Hospital workload by site of disease, expressed as a percentage of workload, April 1983-March 1984.

CONSULTATIVE AND FOLLOW-UP CLINICS

The distribution of these clinics reflects the general zones of service of the Foundation's Regional Cancer Centres in Hamilton, Kingston, London, Ottawa, Thunder Bay and Windsor; and of the Princess Margaret Hospital, Toronto.

HAMILTON

- | | |
|------------------|-----------------------------------|
| Brantford | — St. Joseph's Hospital |
| Cambridge (Galt) | — Cambridge Memorial Hospital |
| Guelph | — Guelph General Hospital |
| St. Catharines | — St. Catharines General Hospital |
| Welland | — Welland County General Hospital |

KINGSTON

- | | |
|---------|-----------------------------|
| Trenton | — Trenton Memorial Hospital |
|---------|-----------------------------|

LONDON

- | | |
|------------|---|
| Chatham | — Public General Hospital |
| Kitchener | — Kitchener-Waterloo Hospital |
| London | — Victoria Hospital, Westminster Campus |
| Owen Sound | — General and Marine Hospital |
| Sarnia | — St. Joseph's Hospital and Sarnia General Hospital |
| Stratford | — Stratford General Hospital |
| Wingham | — Wingham and District Hospital |
| Woodstock | — Woodstock General Hospital |

OTTAWA

- | | |
|----------|---|
| Cornwall | — Cornwall General Hospital and Hotel Dieu Hospital |
| Pembroke | — Pembroke Civic Hospital |

THUNDER BAY

- | | |
|-----------|-------------------------------|
| Geraldton | — Geraldton District Hospital |
|-----------|-------------------------------|

TORONTO

- | | |
|------------------|------------------------------------|
| North Bay | — North Bay Civic Hospital |
| Owen Sound | — General and Marine Hospital |
| Peterborough | — St. Joseph's Hospital |
| Sault Ste. Marie | — Plummer Memorial Public Hospital |
| Sudbury | — Laurentian Hospital |
| Timmins | — St. Mary's Hospital |

WINDSOR

- | | |
|------------|---|
| Leamington | — Leamington District Memorial Hospital |
|------------|---|

**CLINICAL CONSULTANTS
AT THE OCTRF REGIONAL CANCER CENTRES
AND THE PRINCESS MARGARET HOSPITAL**

(As at December 31, 1984)

OCF Hamilton Centre:

M. Ali, M.D.
S. Archibald, M.D.
H. W. Beattie, M.D.
A. M. Bengier, M.D.
W. F. Bennett, M.D.
I. W. Blackstone, M.D.
M. Brain, M.D.
P. Brown, M.D.
A. J. Campbell-Moscrop, M.D.
B. Clark, M.D.
D. Clark, M.D.
J. Collins, M.D.
I. R. Davis, M.D.
P. B. Dent, M.D.
B. Findlay, M.D.
J. D. Gowing, M.B., B.S.
M. Gross, M.D.
R. A. Hadden, M.D.
J. Harvey, M.D.
D. A. Hitch, M.D.
G. K. Ingham, M.D.
B. S. Jackson, M.D.
P. Jenkin, M.D.
J. Kearns, M.D.
P. Knight, M.B., Ch.B.
G. A. Lane, M.D.
E. J. Latimer, M.D.
J. A. McBride, M.B., Ch.B.
R. Meyer, M.D.
W. Nicholson, M.B., B.S.
S. E. O'Brien, M.D.
G. O'Connell, M.D.
W. L. Orovan, M.D.
J. T. Roberts, M.B., Ch.B.
D. Rosenthal, M.D.
D. Sauder, M.D.

B. Trossinan, M.D.
P. Vasarinsh, M.D.
I. Walker, M.D.
W. E. C. Wilson, M.D.
C. Woolever, M.D.
J. E. M. Young, M.D.

OCF Kingston Centre:

J. M. Blakeman, M.D.
J. A. Carmichael, M.D.
W. E. N. Corbett, M.D.
D. Dexter, M.D.
S. F. Hall, M.D.
J. W. Kerr, M.D.
K. W. Mackie, M.D.
J. R. McCorriston, M.D.
R. J. Riopelle, M.D.
D. M. Robertson, M.D.
H. D. Steele, M.D.
E. E. Sterns, M.D.
K. Taguchi, M.D.
D. M. L. Williams, M.D.

OCF London Centre:

H. H. Allen, M.D.
W. B. Barton, M.D.
J. Chertkow, M.D.
J. Coles, M.D.
G. DeRose, M.D.
L. L. DeVeber, M.D.
A. A. Drieger, M.D.
J. Duff, M.D.
C. A. Dyson, M.D.
R. Finley, M.D.
K. Gay, M.D.
D. Girvan, M.D.
R. E. Greenway, M.D.

J. Harris, D.D.S.
 H. Heeneman, M.D.
 D. A. MacKenzie, M.D.
 R. M. McFarlane, M.D.
 T. D. McLarty, M.D.
 J. Nisker, M.D.
 I. D. F. Schofield, D.D.S.
 R. Shearer, M.D.
 M. Smout, M.D.
 W. K. Stavrakys, M.D.
 J. Wyatt, M.D.

OCF Ottawa Centre:

R. P. Abele, M.D.
 D. J. Addison, M.B., Ch.B.
 G. Armstrong, M.D.
 E. A. Atack, M.D.
 J. W. Atkinson, M.D.
 G. G. Barber, M.D.
 M. G. Bard, M.D.
 R. Barr, M.B., Ch.B.
 P. T. Barron, M.B., Ch.B.
 A. W. Barry, M.D.
 P. Beaudry, M.D.
 J. M. Belanger, M.D.
 R. Belanger, M.D.
 D. N. Bell, M.D.
 M. Bell, M.D.
 M. E. A. Bell, M.D.
 C. Benedict, M.D.
 B. Benoit, M.D.
 P. Benoit, M.D.
 J. M. Beresford, M.B., Ch.B.
 J. Bormanis, M.D.
 A. G. Bouchard, M.D.
 M. E. Bourke, M.D.
 R. Boutin, M.D.
 M. Brazeau, M.D.
 B. Burns, M.D.
 L. Busque, M.D.
 P. Capello, M.D.
 C. C. Carruthers, M.D.
 C. B. Cattran, M.D.
 C. Chadwick, M.D.

C. K. Chew, M.D.
 G. C. Cimone, M.D.
 J. C. Clark, M.D.
 J. Collins, M.D.
 G. G. Copestake, L.R.C.P. (U.K.)
 J. M. Cowan, M.B., Ch.B.
 A. Crepeau, M.D.
 H. Curry, M.D.
 I. Dardick, M.D.
 Y. de la Bastide, L.R.C.P. (U.K.)
 G. de la Salle, M.D.
 J. J. Deneault, M.D.
 J. P. Des Groseilliers, M.D.
 J. E. Devitt, M.D.
 C. Don, M.B., B.S.
 J. Drouin, M.D.
 P. Drouin, M.D.
 P. Dubois, M.D.
 F. A. Duggan, M.D.
 R. H. Elder, M.D.
 C. Ellis, M.D.
 R. Elliott, M.D.
 R. H. Ferguson, M.D.
 R. J. Fairfull-Smith, M.B., Ch.B.
 J. F. Fielding, M.D.
 J. B. Freeman, M.D.
 S. J. Fremeth, D.D.S.
 S. W. French, M.D.
 N. G. Futter, M.D.
 L. Garnett, M.D.
 E. Gear, M.D.
 J. Gerin-Lajoie, M.D.
 R. G. Gerridzen, M.D.
 A. Giachino, M.D.
 R. R. Gillies, M.D.
 Z. Grahovac, M.D.
 J. E. Green, M.D.
 D. Grimes, M.D.
 A. Guberman, M.D.
 J. J. Hadju, D.D.S.
 P. Hamilton, M.D.
 A. Haq, M.D.
 J. Hardie, B.D.S.
 I. Hart, M.B., Ch.B.

- J. Henderson, M.B., Ch.B.
 R. Heringer, M.D.
 A. Heron, M.D.
 C. Hetenyi, M.D.
 D. P. Hill, M.D.
 R. B. Hladkiewicz, M.D.
 D. Hooper, M.D.
 E. Hsu, M.D.
 L. B. Huebsch, M.D.
 H. Hugenholtz, M.D.
 G. Hurteau, M.D.
 J. B. Hurtig, M.D.
 A. H. Irvine, M.D.
 R. Jackson, M.D.
 T. G. Jones, M.B., B.S.
 B. Kirk, M.D.
 S. P. Kucey, D.D.S.
 K. Kuwayti, M.D.
 B. Lach, M.D.
 G. Laframboise, M.D.
 J. E. Laws, M.D.
 C. Leahy, M.D.
 B. M. Lefebvre, M.D.
 B. Leonard, M.D.
 E. Liepa, M.D.
 J. B. Lightford, D.D.S.
 L. Lu-Godbout, M.D.
 B. Luke, M.D.
 P. C. MacEwen, M.D.
 B. J. MacInnis, M.D.
 J. P. MacLeod, M.D.
 N. Mayer, M.D.
 W. T. E. McCaughey, M.B., Ch.B.
 R. W. McIntyre, M.B., B.S.
 W. M. McIntyre, M.D.
 D. E. McKay, M.D.
 N. V. McPhail, M.D.
 S. Meban, M.B., Ch.B.
 S. Mercer, M.D.
 N. Z. Mikhael, M.D.
 G. Mintsoulis, M.D.
 D. Moors, M.D.
 J. E. Mullens, M.D.
 J. P. Murnaghan, M.D.
 R. Nelson, M.D.
 P. F. Odell, M.D.
 M. Orizaga, M.D.
 H. Oxorn, M.D.
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 F. M. Shamji, M.D.
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 M. Silverman, M.D.
 D. S. Skene, M.D.
 R. K. Smiley, M.D.
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 B. T. Tsang, M.D.
 G. N. W. Tse, M.D.
 H. K. Uhthoff, M.D.
 F. W. Vaillancourt, M.D.
 V. Walley, M.D.
 W. G. Walsh, M.D.
 J. H. Walters, M.D.
 H. Warnes, M.D.
 A. G. Watson, M.D.
 C. Watters, M.D.
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 L. R. Harnick, M.D.
 G. D. Hart, M.D.
 D. E. Hastings, M.D.
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 C. Hegarty, M.B., B.Ch.
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 J. L. M. Bean, M.D.
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 M. E. Blackstein, M.D.
 T. D. R. Briant, M.D.
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 D. P. Bryce, M.D.
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 G. N. Burrow, M.D.
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 M. Scott, M.D.
 J. S. Senn, M.D.
 M. Silberfeld, M.D.
 E. R. Simpson, M.D.
 G. Foster Smith, M.D.
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 H. A. Smythe, M.D.
 M. J. Sonley, M.D.
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 J. Trachtenberg, M.D.
 M. L. S. Vachon, Ph.D.
 C. P. Vernon, M.D.
 R. Volpe, M.D.
 C. P. N. Watson, M.D.
 N. A. Watters, M.D.
 G. D. Webb, M.D.
 R. H. Wilkinson, M.D.
 C. C. Williams, M.D.
 D. R. Wilson, M.D.
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 A. Zipursky, M.D.
 R. M. Zuker, M.D.

SPECIAL SERVICES



PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources. In 1983, the drug service provided medications for 1456 patients.

As the number of Ontario residents covered by prescription drug insurance plans (including the Ontario Drug Benefit Plan) continues to rise, the number of patients served by the Foundation's drug service has been decreasing.

TABLE I
Patients Served and Prescription Volume
1974-1983

Year	Patients			Prescriptions
	New*	Old**	Total	
1974	1,974	1,909	3,883	17,119
1975	1,868	1,811	3,679	16,771
1976	1,722	1,499	3,221	14,702
1977	1,225	1,147	2,372	12,501
1978	1,113	1,108	2,221	12,183
1979	846	911	1,757	10,312
1980	775	860	1,635	9,398
1981	771	801	1,572	9,803
1982	769	932	1,701	9,252
1983	714	742	1,456	9,212

*A "new" patient is one who has received drugs for the first time ever.

**An "old" patient is one who previously was registered in the drug service.

The total cost of the drug service in 1983 was \$450,872.94 — an increase of 20% from the \$375,971.20 in the previous year (Table II). The cost per patient has increased to \$309.67 in 1983 from \$221.03 in 1982. The cost per prescription has increased to \$48.94 in 1983 from \$40.64 in 1982.

TABLE II**Cost of Drug Service
1974-1983**

Year	Payments for Drugs	Total Cost of Drug Service
1974	206,189.41	208,541.66
1975	214,942.30	216,055.35
1976	175,949.99	177,984.37
1977	148,418.40	152,021.06
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97
1982	370,388.28	375,971.20
1983	448,401.93	450,872.94

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for *confirmed* cases of cancer and the steroid-receptor assays for *confirmed* cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

During the fiscal period April 1, 1983 to March 31, 1984, 4,116 steroid-receptor assays and 36,445 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre 1200 Main Street West Hamilton, Ontario L8S 4J9 tel: (416) 525-9140	Dr. E. D. Ryan
Kingston General Hospital Stuart Street Kingston, Ontario L7L 2V7 tel: (613) 547-2121	Dr. A. F. Clark
Victoria Hospital 375 South Street London, Ontario N6A 4G5 tel: (519) 432-5241	Dr. E. R. Tustanoff
Ottawa Civic Hospital 1053 Carling Avenue Ottawa, Ontario K1Y 4E9 tel: (613) 729-2511	Dr. C. Lapkoff
General Hospital of Port Arthur 460 North Court Street Thunder Bay, Ontario P7A 4X6 tel: (807) 344-6621	Dr. F. J. Lone
Sunnybrook Medical Centre 2075 Bayview Avenue Toronto, Ontario M4N 3M5 tel: (416) 486-3626	Dr. A. Malkin

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre

1200 Main Street W.

Hamilton, Ontario L8S 4J9 tel: (416) 525-9140

Dr. E. D. Ryan

Victoria Hospital

375 South Street

London, Ontario N6A 4G5 tel: (519) 432-5241

Dr. E. R. Tustanoff

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1053 Carling Avenue

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Dr. D. J. A. Sutherland

University of Toronto

Medical Sciences Bldg., Rm. 7336

Toronto, Ontario M5S 1A8 tel: (416) 978-3553

Dr. G. E. Mobbs

DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1983, 4676 specimens were submitted by dentists (5089 in 1982).

The number of reports voluntarily submitted by the directors of pathology departments has continued to increase and, in 1983, 47,560 reports were submitted, a 5% increase over the 45,048 reports submitted in 1982.

These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation administers and funds the operation of five lodges for out-of-town ambulatory cancer patients attending the Regional Cancer Centres for diagnosis and treatment. These lodges provide comfortable, supportive accommodation, with minimal supervision, at no cost to the patient. Escorts are accommodated at minimal cost when beds are available.

The Foundation provides this accommodation because location of the treatment centres often requires the patient to travel a considerable distance; without these facilities, the patient would require hospitalization at far greater expense to the Province.

The table below shows the current facilities, the number of beds and the patient days spent in each lodge during the fiscal year ended March 31, 1984.

		Number of Beds	Patient Days
KINGSTON	Quinte-Thousand Islands Lodge	26	4,715
LONDON	Thameswood Lodge	50	7,845
OTTAWA	Maurice J. Grimes Lodge	36	6,890
THUNDER BAY	Amethyst House Lodge	18	2,399
TORONTO	Princess Margaret Hospital Lodge	105	24,267

In Hamilton, construction has started on a new lodge on the grounds of Henderson General Hospital to accommodate patients attending the Hamilton Regional Cancer Centre. Opening in 1985, the new lodge will accommodate 20 patients, although the structure will contain shelled-in space, to be completed as necessary, for a further 18 patients.

Patients who require hostel accommodation while being treated at the Toronto-Bayview Regional Cancer Centre are housed in facilities offered, on a temporary arrangement, by Sunnybrook Medical Centre; 892 patient days were recorded in this fiscal year.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation to one of its Regional Cancer Centres or to the Princess Margaret Hospital of those patients who live more than 25 miles from the centre and are considered to be in financial need. For patients 18 years or less, transportation is provided to the principal pediatric oncology treatment centres in the five health science complexes, namely:

- Hamilton — McMaster Medical Centre
- Kingston — Kingston General and Hotel Dieu Hospitals
- London — War Memorial Children's Hospital, Victoria Hospital Corporation
- Ottawa — Children's Hospital of Eastern Ontario
- Toronto — Hospital for Sick Children

Usually transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1984, the total cost for transportation of patients was \$478,815, compared to \$349,793 for the fiscal year ended March 31, 1983.



RESEARCH PROGRAMS



SUMMARY OF OCTRF RESEARCH

Grants-in-Aid

1984 marked the end of one of the Foundation's oldest research efforts — the grants-in-aid program. This program, which was initiated in 1945 to support research projects, was terminated in 1982, although, to provide "bridge" support until funding was received from another agency, grantees were allowed to use any unexpended funds until March 31, 1985. Since the program started, the Foundation approved and funded 471 projects. At the outset, we supported both basic or clinical research, but in 1950 it was agreed that the National Cancer Institute of Canada would support basic research and the OCTRF would support clinical cancer research. From 1945 until the mid 1970s, the Foundation was able to support almost 100% of the projects recommended for funding by the grants' review panels and the Research Committee on the basis of scientific merit. Unfortunately, although the Foundation used a significant amount of its reserves, it became increasingly difficult to maintain this level of support because of inflationary pressures and an increasing number of applications. In 1977, the Foundation received an award of \$2,000,000 from the Ontario Ministry of Health, through provincial lottery funds, which enabled it to continue the grants-in-aid program for a few more years. However, in 1981 the Board, recognizing the difficulties in maintaining the grants program and the need for additional research scientists, decided to phase out the grants-in-aid program and to use these funds to recruit additional research scientists for the regional cancer centres and the health sciences complexes. The Foundation is keenly aware of the difficulties that research scientists encounter in obtaining operating grants and hopes that at some time in the future the Ministry will approve additional funding for a limited grants-in-aid program.

Career Scientists

As reported last year, the Foundation, in accord with its decision to recruit additional research scientists, established a subcommittee of the Research Committee to review applications for the appointment (and reappointment) of career scientists in the regional cancer centres and research associates scholars in the health sciences centres. This committee reviews the recommendations of the Director of the regional cancer centre and the Dean of the affiliated university regarding the appointment of candidates to work in the centre(s) as career scientists. After due consideration, the committee makes a recommendation to the research committee and/or board regarding the appointment. The subcommittee has been active during 1984 and, as a result, six career scientists were appointed. Of these, four are working in the centres

— one in London, two in Hamilton, and one in Ottawa. Two others will commence their duties in 1985 — one in Kingston effective January 1, and one in Ottawa effective April 1.

Research Associates

The Foundation continues to support seven research associates in the health sciences centres — one in Hamilton, five in Toronto, and one in London, on a full or part-time basis. Continuing salary support for research associates depends upon the maintenance of peer-reviewed grant support, publications in peer-reviewed journals and periodic site reviews.

Research Scholars

In 1983, the Subcommittee on Support of Research Personnel recommended that the Foundation discontinue the research associates' program, and establish a research scholarship program. The major difference between these two programs is that research associates had a "life-time" appointment dependent upon the maintenance of specified requirements, whereas research scholars were supported for a five-year term, once renewable. They were required to maintain the same standards as associates and spend at least 75% of their time on research. In recommending this change, the committee agreed that research associates would continue to be supported under the guidelines of their original appointment. A research scholarship competition, held in October 1983, attracted six applications from deans on behalf of candidates whom they deemed worthy. The Subcommittee on Support of Research Personnel reviews these applications and makes recommendation based on the merit of the applicant. As a result of the 1983 competition, a candidate from the University of Western Ontario was appointed and is working now in the Department of Nuclear Medicine at the Victoria Hospital, London. In addition to salary support, he was given a one-time award (\$5000) to assist him to set up his laboratory. A second research scholarship competition, held in October 1984, drew four applications. The recommendations of the Subcommittee will be presented to the Research Committee and the Board early in 1985 and appointment(s) will become effective July 1, 1985.

Senior Scientific Staff at the Ontario Cancer Institute

In addition to the career scientist and the research associate/scholarship programs, the Foundation provides salary support for the senior scientific staff in the Departments of Biology and Physics at the Ontario Cancer Institute.

Core Support

The Foundation also provides secretarial support and funding for the "in-common" needs of the career scientists working in the Foundation's regional cancer centres. Applications for this support are submitted by the director of the centre and subse-

quently are reviewed by the Subcommittee and the Research Committee before being presented to the Board for final approval.

Publications

A list of articles and abstracts published by grantees, career scientists, and research associates is appended in Appendix B.

Reports of a number of the funded projects are included in this section.

Mary Parkes
Research Secretary

The Ontario Clinical Oncology Group

In the summer of 1982, the Research Committee established this clinical trials group with seed funding obtained through a grant from the Ontario Provincial Lottery. The co-ordinator is Dr. P. B. McCulloch and the biometry and methodology centre is the Department of Clinical Epidemiology and Biostatistics at McMaster University Medical School.

The Policy Committee has a representative from each regional cancer centre, the Ontario Cancer Institute, and each medical school. In 1983 and again in 1984, approximately 300 individuals were invited to submit brief proposals for clinical trials. The first 25 submitted were peer reviewed, and two were chosen for expansion and activation in 1983 or 1984. Two clinical trials have been activated.

The principal investigator in the first trial is Dr. Roy Clark of the OCI. This trial involves women with small primary breast cancers, deemed surgically disease-free after limited resection of the tumor; in these women the axillary-node dissection showed no pathologic involvement. After informed consent, such patients are randomized to receive local radiotherapy to the affected breast or observation alone. This trial should answer important questions concerning the effects of such adjuvant radiotherapy on local and distant recurrence, long-term survival and quality of life.

The principal investigator of the second trial is Dr. Mark Levine of the Hamilton Regional Cancer Centre. This trial involves women with a higher risk of relapse than those patients in Dr. Clark's study because they had involvement of the axillary lymph nodes following their primary breast surgery. They are clinically disease-free, but shortly after surgery, following informed consent, the patients are randomized to receive a short (three months) course of intensive chemohormonal therapy or a longer more conventional (nine months) course of chemohormonal therapy. The primary focus concerns disease-free and overall survival, but it should provide important data concerning quality of life and relative costs.

The OCI and nearly all of the regional cancer centres are entering patients in one or both of these trials and, as of December 1984, they have enrolled over 200 patients — a result that shows a high degree of enthusiasm.

Several new draft proposals are being peer reviewed. By continuous consultation the Foundation is maintaining close contact with the NCIC's Clinical Trials Group to avoid duplication of effort. The Ontario group hopes to activate one or two new Ontario-wide clinical trials in 1985. The lottery funds only are sufficient to act as seed money for new clinical trials. The Medical Research Council already is supporting one of these active breast cancer trials but the completion of any new clinical trials will call for the infusion of external funds. In the spring of 1985 we plan a three-day workshop at McMaster University to stimulate clinical investigators from around the province to illustrate how to ask and answer questions relating to cancer care.

This new group is off to a good start as evidenced by good patient entry into the two established trials and the many suggestions received for new trials; thus the future for co-operative clinical investigation in this province appears to be bright.

P. B. McCulloch, M.D., F.R.C.P.(C)
Program Co-ordinator

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REPORTS ON RESEARCH PROJECTS

HAMILTON

McMaster University:

- | | |
|---|-----|
| Oncofetal Antigens Detected by Serum
from Pregnant Women
P. B. Dent and S. K. Liao | 110 |
| Absorption and Metabolism of Equine Estrogens
in Normal Men and Postmenopausal Women
B. R. Bhavnani and C. A. Woolever | 112 |
| Biochemistry and Histology of Endometrial Carcinoma
in Relation to Endogenous and Exogenous Hormones
C. A. Woolever, B. R. Bhavnani and P. N. Lagrotteria | 113 |
| Presence and Regulation of Gap Junctions
in Cancerous and Noncancerous Tissues
R. E. Garfield and D. R. Inman | 115 |

OCF Hamilton Regional Cancer Centre:

- | | |
|---|-----|
| Development of Light Dosimetry
for Photodynamic Therapy
B. C. Wilson and W. P. Jeeves | 116 |
| Additional Investigations | 118 |

KINGSTON

OCF Kingston Regional Cancer Centre:

- | | |
|--|-----|
| Hematoporphyrin Derivative Photoradiation
Therapy for Cancer
J. C. Kennedy | 120 |
|--|-----|

Queen's University:**Sequential Monitoring of Natural Killer (NK)
Cell Activity in Cancer Patients**

A. Morales 121

Nerve Growth Factor and Neurofibromatosis

R. J. Riopelle 122

LONDON**OCF London Regional Cancer Centre:****Investigation of Physical Radiation Parameters**

D. J. Dawson 123

**Combined Modality Treatment of Cancer
Using Multicell Spheroids**

W. R. Inch 124

**Surface Antigens of Cultured Human Astrocytomas:
Identification and Interpretation of Subsets**

J. G. Cairncross 125

In Vivo Models of Tumor Growth and Metastasis

A. F. Chambers 126

Additional Investigations 127**University of Western Ontario:****A Cohort Study of the Effect of Age at First Full-Term
Birth upon the Risk of Death from Breast Cancer**K. M. Stavraky, M. E. Smith, A. E. Donner
J. R. Miller and S. H. Uh 131**The Effect of Socioeconomic Status on the Prognosis
of Cancer of Various Sites**

K. M. Stavraky and J. E. Kincade 132

OTTAWA**OCF Ottawa Regional Cancer Centre:**

Clinical Investigations	133
--------------------------------------	------------

TORONTO**Hospital for Sick Children:**

Intermediate Filament Proteins as Markers in Pediatric Malignancies	
R. Bauman, M. J. Phillips, C. R. Smith and H. Yeger	135

**Ontario Cancer Institute incorporating the
Princess Margaret Hospital:**

Leukemia Program at the Ontario Cancer Institute	
E. A. McCulloch and J. E. Curtis	136

Classification of Survival Curves	
A. Ciampi	138

Clinical Trials Secretary for Gastrointestinal Tumor Group	
B. J. Cummings and G. DeBoer	139

Clinical Trials in Breast Cancer	
R. M. Clark, N. F. Boyd, U. Ambus and K. I. Pritchard	140

A Phase III Clinical Trial of Misonidazole and Radiation Therapy	
G. M. Thomas	141

Investigation of a Stem-Cell Model of Human Tumor Growth	
R. N. Buick, A. Ciampi and J. E. Till	142

OCF Toronto-Bayview Regional Cancer Centre:**Characterization of Culture-Induced Cytotoxicity (CIC)
among Natural Killer Cell-Depleted, Human Peripheral
Blood Lymphocyte Subpopulations**

J. J. Rusthoven and D. Osoba 144

Additional Investigations 145**University of Toronto:****Hormonal Control of Prostatic Cancer**

B. G. Mobbs 148

The Irradiated Larynx and Voice

M. L. Stoicheff 150

**Construction and Testing of Coded-Aperture
Collimation System for Gamma-Ray Cameras**

M. L. G. Joy 151

A Research Program in Adult Leukemias

M. A. Baker 152

WINDSOR**OCF Windsor Regional Cancer Centre:****Clinical Investigation** 153

McMaster University, Hamilton**ONCOFETAL ANTIGENS DETECTED BY SERA
FROM PREGNANT WOMEN***P. B. DENT** and S. K. LIAO†, *Hamilton, Ontario*

We have been studying the immunological aspects of human melanoma to determine if tumor-associated antigens can be used to manage patients with this disorder. We have shown that sera from patients with cancer and from pregnant or postpartum women contain antibodies, which react preferentially with tumor cells. However the spectrum of reactivity is so broad and complex that we concluded it was unlikely that such sera could be used to identify antigens, which would be widely applicable clinically (*Cancer in Ontario* 1983: 117).

With the advent of the monoclonal antibody technique, we have in hand a more promising tool for immunodiagnostic and immunotherapeutic purposes. Our laboratory has studied two such antibodies, which we have raised against melanoma cells. The first, 140.240, defines an epitope that is present on virtually all melanoma cells and on some fetal tissues but not on other cancers and normal tissues. The second, 140.72, reacts with an epitope that is found on most melanoma cells and a variety of cancers, which produce carcinoembryonic antigen (CEA). The epitope is present on the classical CEA molecule of 200 kd molecular weight (not present on melanoma), and on a smaller molecule (95-150 kd), which is present on melanoma cells.

Our present work is directed at the characterization of the antigen molecules identified by these monoclonal antibodies, the use of the antibodies in detecting tumor antigens in the circulation, and in tumor imaging and immunotoxin therapy. Preliminary results using these antibodies to detect antigen in the circulation indicate that antigen detected by 140.72 (CEA cross-reactive antigens) are present in 3% of normal individuals (1/28), 10% of cancer patients with normal CEA levels (3/29), and 50% of cancer patients with elevated CEA levels (15/30). These studies have been done in collaboration with Dr. E. Ryan of Department of Pathology at McMaster University.

*Project 276. (Final Report)

**Professor of Pediatrics and Pathology, McMaster University, Hamilton; and Consulting Immunologist, OCF Hamilton Regional Cancer Centre.

†Associate Professor of Pathology and Pediatrics, McMaster University; and Research Associate, OCF Hamilton Regional Cancer Centre.

With the termination of the Ontario Treatment and Research Foundation grants-in-aid program, we have sought funding from other sources for the continuation of these studies. Future work will involve the refinement of antigen-assay procedures to increase their sensitivity, and the evaluation of the clinical relevance of the information so obtained.

ABSORPTION AND METABOLISM OF EQUINE ESTROGENS IN NORMAL MEN AND POSTMENOPAUSAL WOMEN*

B. R. BHAVNANI** and C. A. WOOLEVER**

Hamilton, Ontario

In continuation of our studies dealing with the equine estrogens and their metabolic fate in postmenopausal women, we have investigated the following: Development of a method for the synthesis of $[4-^{14}\text{C}]$ -labelled equilin.

This material is needed to correct for procedural losses incurred during the purification and isolation of ^3H equilin and ^3H equilin sulfate following the administration of these steroids to postmenopausal women. In this synthesis 50 μCi of $[4-^{14}\text{C}]$ dehydroepiandrosterone acetate (1.0 mg) were dissolved in 10 ml of petroleum ether (b.p. 60-80°C) and then treated with 18 mg of dibromodimethyl hydantoin. The mixture was refluxed for 30 minutes, cooled and filtered. The filtrate was extracted with CCl_4 and the residue obtained after removal of CCl_4 was dissolved in 7 ml of *S*-collidine and the solution heated for 15 minutes at 140°C under nitrogen. The $[4-^{14}\text{C}]$ 7-dehydroepiandrosterone formed was extracted with ether and purified by HPLC using the system acetonitrile: water: acetic acid (60:39:1) and a ultra-sphere-ODS column. A total of 10 μCi of pure $[4-^{14}\text{C}]$ 7-dehydroepiandrosterone was obtained. This material was converted to $[4-^{14}\text{C}]$ equilin by aromatization with human placental preparation as follows:

Human placenta (560 g) was homogenized in a waring blender with 360 ml of sucrose buffer (0.25M sucrose, 0.05M phosphate buffer, pH 7.0 and 0.04M nicotinamide). The homogenate was centrifuged at 10,000 $\times$ g and the supernatant was used for aromatization of 7-dehydroepiandrosterone. A total of 200 μg (20×10^6 dpm) of $[4-^{14}\text{C}]$ 7-dehydroepiandrosterone was mixed with 10ml of the 10,000 $\times$ g placental supernatant, 10 μ moles of ATP. The mixture was incubated for 1 hour under 95% oxygen and 5% CO_2 . The $[4-^{14}\text{C}]$ equilin formed was extracted with ethyl acetate and purified by paper chromatography and HPLC. The radiochemical purity of $[4-^{14}\text{C}]$ equilin was found to be over 95% pure, when checked by the isotopedilution technique.

This material will be used as a marker for procedural losses in our studies dealing with the pharmacokinetics of equilin and equilin sulfate in postmenopausal women.

*Project 388.

**Professor of Obstetrics and Gynecology, McMaster University, Hamilton.

BIOCHEMISTRY AND HISTOLOGY OF ENDOMETRIAL CARCINOMA IN RELATION TO ENDOGENOUS AND EXOGENOUS HORMONES*

C. A. WOOLEVER**, B. R. BHAVNANI** and P. N. LAGROTTERIA†
Hamilton, Ontario

This study examined the inter-relationship between the steroid hormone receptor status of the endometrium and various hormone-related enzymatic activities, namely, (a) 17 β -hydroxysteroid dehydrogenase, (b) arylsulfotransferase, (c) 20 α -hydroxysteroid dehydrogenase, and (d) ornithine decarboxylase. The results obtained in this study permitted the following conclusions:

- 1) Tissues with evidence of estrogenic stimulation (or progesterone deficiency), i.e. normal proliferative and hyperplastic endometrium, are characterized by relatively high steroid hormone receptor concentrations. Endometrial carcinoma and normal secretory endometrium have a low steroid hormone receptor content.
- 2) 17 β -hydroxysteroid dehydrogenase, 20 α -hydroxysteroid dehydrogenase and arylsulfotransferase activities are progesterone-induced enzymes. Their activities are highest in normal secretory endometrium. No differences in the activities of these enzymes are seen among proliferative, hyperplastic and carcinomatous tissues. The latter three tissue types are each exposed to a hormonal environment characterized by the absence or lack of progesterone. Identical Michaelis-Menten constants (apparent Kms) were obtained for the 17 β -HSD and 20 α -HSD enzymes, supporting previous suggestions that the two activities are localized at one enzyme.
- 3) When the activities of the above progesterone-induced enzymes are elevated, the metabolism of estradiol is increased. The products of estradiol metabolism (i.e. estrone and estrone sulfate) have a poor affinity for the estradiol receptor and thus, the estrogenic effects on the endometrium are reduced.
- 4) Because of increased estradiol metabolism, there will be a decrease in the estrogen-induced synthesis of estradiol and progesterone receptors. Nonetheless, correlation coefficients calculated to examine the relationships between the enzyme and receptor status of the endometrium did not reveal the inverse association.
- 5) Ornithine decarboxylase activity was greater in normal proliferative ($p < 0.05$) than in normal secretory endometrium. However, ODC activity was not elevated in hyperplastic tissues and the activity in carcinomatous endometrium was very

*Project 439.

**Professor of Obstetrics and Gynecology, McMaster University, Hamilton.

†Graduate Student.

similar to the activity in proliferative endometrium. Therefore, ODC activity did not prove to be a good marker for endometrial cancer.

- 6) The elevated 17 β -HSD, 20 α -HSD and ASFT activities in secretory endometrium (high progestational phase) indicate that the effectiveness of progestin therapy in cancer of the endometrium may be partially mediated via the progesterone receptor mechanism leading to the induction of enzymes involved with estradiol metabolism. These findings encourage further studies of methods for maintaining or improving the responsiveness of endometrial tumors to progestin therapy and/or progesterone plus antiestrogens (e.g. tamoxifen).

PRESENCE AND REGULATION OF GAP JUNCTIONS IN CANCEROUS AND NONCANCEROUS TISSUES*

R. E. GARFIELD** and D. R. INMAN**, *Hamilton, Ontario*

It is postulated that growth and proliferation of cells depend in some way on the gap junctions — specialized cell-to-cell contacts to provide the means for direct inter-cellular communication. The ultrastructural research described here was undertaken:

- To determine the relative abundance of gap junctions in normal and cancerous human breast tissues.
- To explore the relationship between the growth of myometrium and the control and regulation of gap junctions in response to steroid hormones.

By thin-section electron microscopy we examined normal and malignant human breast tissue samples and myometrial tissues from immature rats following treatment with steroid hormones.

Gap junctions and desmosomes (cell-to-cell contacts characteristic of epithelial cells) were found between cells of the mammary ducts in all normal human breast samples. In all mammary tumors, however, no gap junctions were found although the frequency of desmosomes appeared normal. Gap junction development in the myometrium was stimulated by estradiol; when progesterone was administered simultaneously, however, it was suppressed. In the myometrium, estradiol induced increased hyperplasia and hypertrophy, which preceded gap junction development.

Our preliminary conclusions are:

- Gap junctions appear to be absent from human breast cancer cells although they are present in normal breast.
- The resulting lack of direct cell-to-cell communication may be one of the mechanisms underlying uncontrolled tumor growth.
- Growth and gap-junction development in the rat uterus appear to be regulated by steroid hormones and prostaglandins.
- The absence of gap junctions appears to be necessary for uterine growth.
- Growth of the uterus may in part be necessary for the presence of gap junctions.

*Project 458.

**Professor of Neurosciences, McMaster University, Hamilton.

**Hamilton Regional Cancer Centre****DEVELOPMENT OF LIGHT DOSIMETRY
FOR PHOTODYNAMIC THERAPY***

B. C. WILSON** and W. P. JEEVES†, *Hamilton, Ontario*

We are developing methods of radiation dosimetry of visible light in tissue as part of a research and clinical program in photodynamic therapy (PDT). In PDT, the tumor is irradiated with high intensity visible light after intravenous administration of a photosensitizing drug^{1,2}. The aims of the dosimetry study are: (a) to examine the factors determining the propagation of light in living tissues; and (b) to establish techniques for calculating and measuring the distribution of absorbed light energy in target tissue volumes, in order to optimize irradiation procedures for individual patients.

We have built a computer-controlled scanning spectroradiometer, which uses, as photon detectors, optical fibers that can be positioned stereotactically within irradiated tissue to measure the light absorption and scattering properties *in vivo*. To date studies done in various animal tissue models have demonstrated the strong wavelength dependence of light attenuation, and the significant effect on this of blood concentration and oxygenation³.

These tissue data are being used to design "phantom" materials to simulate the optical properties of tissue; these phantoms will permit more detailed measurements of light distribution than is possible *in vivo*. These phantom measurements are then used to check experimentally the predictions of a theoretical model of light propagation in tissue, which is being developed using a Monte Carlo computer technique⁴.

Even at this early stage, these studies are contributing to the design and calibration of clinical light delivery systems for specific tumor sites such as the brain.

*Project 452.

**Chief Physician, OCF Hamilton Regional Cancer Centre; and Associate Professor of Radiology and Physics, McMaster University, Hamilton.

†Harold E. Johns Post Doctoral Fellow, OCF Hamilton Regional Cancer Centre.

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ADDITIONAL INVESTIGATIONS

Dr. W. M. Hryniuk, Director of the Hamilton Regional Cancer Centre, reports on the following clinical research investigations:

ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

In co-operation with the London Regional Cancer Centre, we are conducting a randomized controlled trial to determine the efficacy of a short, intensive 12-week course of chemohormonal therapy and to compare it with the standard 36-week course of chemotherapy. This trial is supported by the Ontario Clinical Oncology Group and funded by MRC.

QUALITY OF LIFE IN WOMEN RECEIVING ADJUVANT CHEMOTHERAPY FOR STAGE II BREAST CANCER

A new instrument has been developed to measure the impact of chemotherapy in women receiving adjuvant chemotherapy for Stage II breast cancer. This study will determine its validity, reliability and responsiveness. In addition, the utility of the patient's chemotherapy experience is being determined by the time/trade-off technique.

PILOT STUDIES IN STAGE IV BREAST CANCER

A Phase II study is being conducted in women with Stage IV breast cancer to measure the dose intensity of mitoxantrone.

DRUG-SEQUENCE IN CHEMOTHERAPY OF HEAD AND NECK CANCER

Dr. G. Browman is co-ordinating a randomized trial to determine the optimum sequence for the administration of 5-fluorouracil and methotrexate. The trials are designed to test the biochemical model, which describes the interaction of the two drugs. The present sequence embodies an 18-hour delay. This trial is funded through NCIC.

STUDIES IN ACUTE MYELOBLASTIC LEUKEMIA

The Hamilton Centre is part of the Leukemia Intergroup (LIG) — a co-operative group of seven founding centres whose mission it is to seek laboratory and clinical predictors of treatment outcome in acute leukemia. All patients with newly presenting or first-relapse acute leukemia are treated according to the LIG protocol. Laboratory studies are performed on bone-marrow cells and pharmacologic studies on peripheral blood to determine predictors of treatment outcome and duration of remission. These studies are supported by the NCI.

STUDIES IN GYNECOLOGIC MALIGNANCIES

A pilot study has been completed which tested the efficacy of intensive Adriamycin and cis-platinum with autologous bone marrow rescue.

CURRENT STUDIES IN OVARIAN CARCINOMA

We are collaborating with the NCIC with ovarian trials 6, 7 and 8, which include all stages of ovarian carcinoma. The 222 pilot study has been completed and the data were analyzed in mid-November.

Also, we are doing a randomized control trial comparing laser therapy with cryotherapy in the treatment of preinvasive cervical dysplasia. We have received a grant from the Ministry of Health for the development of a DES registry which will look at the impact of diethylstilbestrol on the offspring. This study is in collaboration with the Wellesley Hospital in Toronto.

Finally, funding is ready for a case control study looking at the epidemiology of ovarian carcinoma. The final details of this study, which will be done in collaboration with the NCIC epidemiology unit, remain to be ironed out.

CO-OPERATIVE GROUP TRIALS

We are following selected protocols of the NCIC, OCOG and NSABP for myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, non-small cell carcinoma of the lung, ovarian carcinoma, renal-cell carcinoma, and Stage I breast cancer.

**Kingston Regional Cancer Centre****HEMATOPORPHYRIN DERIVATIVE PHOTORADIATION THERAPY
FOR CANCER***

J. C. KENNEDY**, *Kingston, Ontario*

This final report summarizes results of photoradiation therapy research carried out with OCTRF support between 1977 and 1984.

We were first to report that irreversible neuropathology could follow a single injection of tetraphenylporphine sulfonate — a pure compound that attracted much interest because of its superior tumor-localizing and photosensitizing properties; first to report that treatment with doxorubicin (Adriamycin) as much as a year before the start of photoradiation therapy could induce dangerous skin reactions to standard doses of photoactivating light; first to work out the implications of the cosine correction factor for photoradiation therapy of curved surfaces, and to describe appropriate ways to treat fields whose surfaces approximated various conic sections; first to design, construct, and use light sources capable of treating large curved fields, such as the whole of the anterior chest wall; first to realize the problem of treating fields whose surfaces formed compound curves, and to design, construct, and use diffuse light sources to treat such fields. Also, we were first to demonstrate that, for certain purposes, a slightly modified 35 mm slide projector was a more useful source of photoactivating light than any laser, and first to develop slide-projector, light-delivery systems appropriate for treating various types of tumors in the skin, in the vagina, and in the pelvis immediately adjacent to the vagina. Finally, we were first to report clinical benefit from the combination of hyperthermia and photoradiation therapy. These findings have been transmitted to the photoradiation therapy research community, mainly via a series of invited papers presented at various international symposia.

*Project 441. (Final Report)

**Career Scientist, OCF Kingston Regional Cancer Centre; and Associate Professor of Radiation Oncology and Pathology, Queen's University, Kingston.

Queen's University, Kingston

**SEQUENTIAL MONITORING OF NATURAL KILLER (NK)
CELL ACTIVITY IN CANCER PATIENTS***

A. MORALES**, *Kingston, Ontario*

There is an obvious appeal in the conceptual correlation of tumor rejection in vivo and the ability of lymphoid cells to lyse tumor cells in vitro. The lymphoid natural killer (NK) cells were discovered over a decade ago and it is commonly believed that they represent the first line immunological defense against cancer. There are significant differences in the levels of NK activity between normal individuals, patients with localized cancer and those with disseminated disease (*Cancer* 1983, 52:667). Furthermore, NK is known to be influenced profoundly by immune modulators, i.e. interferon, BCG.

We have employed conventional and whole-blood cytotoxicity assays for in vitro NK activity in a linear fashion to determine their usefulness in monitoring patients with genitourinary neoplasms. Difficulties were encountered due to the lack of an acceptable standard. Therefore, we developed a freezing apparatus and set out to assess the feasibility of using frozen standards performed through three separate freezing processes. Frozen-thawed effector cells were obtained from leukapheresis and through ficoll separations. Multiple experiments were carried out to determine the steps responsible for the loss of activity, and for daily and interassay variations. The addition of DMSO during freezing produced the greatest loss of NK activity; the major influences on the recovery of cytotoxic activity were the duration and temperature of the post-thaw period. Despite careful efforts to correct known adverse influences — pH, temperature, culture media, etc. — we did not achieve consistent same-day replicability.

We have concluded that current assays for NK activity may be valid for short-term monitoring of cancer patients. To date, linear determination of NK activity for prognostic and therapeutic purposes is not feasible because we lack an effective standard by which to correct daily and interassay variations.

*Projects 391 and 460. (Final Report)

**Professor and Chairman, Department of Urology, Queen's University, Kingston, Ontario.

NERVE GROWTH FACTOR AND NEUROFIBROMATOSIS*

R. J. RIOPELLE**, *Kingston, Ontario*

A single neuronal-cell biological assay was used to quantitate neuronal growth factor(s) (NGF) in 87 serum samples from 69 patients in 48 families with von Recklinghausen neurofibromatosis, plus 16 samples from 16 comparison subjects. Mouse NGF was used as a standard for the bioassay, and results of serum assays were expressed as NGF equivalents. Antiserum to mouse NGF produced a partial inhibition of serum-induced neurite outgrowth, while kinetics of neurite outgrowth and maximal cellular response to serum were found to differ from those of mouse NGF. The mean values ($\pm$ S.D.) of neuronal growth factor(s) in serum from the neurofibromatosis (NF) patients were 20.5 ± 15.7 pg/mg serum protein, while mean values for the comparison groups as a whole were 22.3 ± 15.6 pg/mg serum protein. Sex, race/ethnicity, patient age and date of sample collection did not significantly influence serum levels among patients or comparison subjects. Serum levels in three to six serial samples taken from women during the course of pregnancy, during delivery and in the postpartum period did not differ significantly from one time to another.

Explants of 21 neurofibromas from 16 patients with von Recklinghausen neurofibromatosis (NF-I) plus tumor tissue from seven comparison patients and normal tissue from one of the NF-I patients were assayed for neuronal growth factor(s) using dissociated embryonic sensory neurons from chick embryo. Twenty-one of 21 neurofibroma explants released detectable quantities of neuronal growth factors, but only 2 of 8 non-neurofibroma tissue explants released activity.

While antiserum to mouse NGF produced partial inhibition of the neurite outgrowth induced by some of the neurofibromas, overall differences between assays containing antibody and controls reached statistical significance in only three cases; in one case, explants of a separate tumor from the same patient had no detectable NGF-like activity.

These data suggest that human serum contains non-NGF neuronal growth factors, but that the levels of the factors are not high enough to assist in the identification of von Recklinghausen neurofibromatosis patients.

These studies support the hypothesis that local release of neuronal growth factors in neurofibromas are responsible for neurites observed within these tumors, and provide further evidence that endoneurial tissue of peripheral nerve is a rich source of heterogeneous neuronal growth factors.

*Project 443. (Final Report)

**Associate Professor of Medicine (Neurology), Queen's University, Kingston.

**London Regional Cancer Centre****INVESTIGATION OF PHYSICAL RADIATION PARAMETERS***

D. J. DAWSON**, *London, Ontario*

The dose distribution in the penumbral region (edge) of therapeutic x-ray beams must be accurately established to avoid radiation-sensitive organs. This investigation used an extrapolation technique for one dosimetric system, namely ionization chambers of varying geometric configuration, to determine the corrected penumbral dose profiles for beam energies from Co^{60} to 31-MV x-rays. The model proposed considers that there are two distributions in the penumbral region, namely the dose and photon-fluence distribution¹. An ionometric technique has been developed to delineate the photon-fluence distribution and analysed the differences between these distributions to determine the lateral spread of the secondary electrons. Our results indicate that, because of the lateral spread of the secondary electrons, diodes cannot be used to measure penumbral dose distributions for beam energies above Co^{60} and that electron fluence effects, which the present dose computational models do not consider, are important at these higher energies.

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*Project 266.

**Senior Physicist, OCF London Regional Cancer Centre; and Associate Professor of Radiation Oncology, and Sessional Lecturer of Physics, University of Western Ontario, London.

COMBINED MODALITY TREATMENT OF CANCER USING MULTICELL SPHEROIDS*

W. R. INCH** *London, Ontario*

Radiosensitizers are chemicals which have the capacity to increase the lethal effects of ionizing radiation. Ideally, they should increase radiosensitivity without themselves being cytotoxic and they should preferentially sensitize hypoxic malignant cells. The nitroimidazoles have proven to be the best sensitizers and misonidazole is undergoing clinical trials.

Cimetidine, an H_2 blocker, is a hydrophilic molecule with an imidazole ring and a side chain containing a sulphur atom. Recently, we noted unexpected gastrointestinal symptoms in patients, who were receiving radiotherapy to the abdominal cavity, and were also taking cimetidine for duodenal ulcer. This prompted us to investigate its action in combination with ionizing radiation, using the V79 multicell spheroid tumor model.

The toxicity of cimetidine was determined using V79 monolayer cultures, exposing them to 1 and 5 mM of the chemical for up to seven days.

V79 spheroids were grown to a diameter of 600 μ M. Approximately 100 spheroids were transferred to each of three flasks containing 50 ml of fresh medium. Three hours before irradiation the flasks were gassed with 5% oxygen plus 95% nitrogen to make the inner layers of cells acutely hypoxic. One hour before irradiation, we added cimetidine or cimetidine and misonidazole to the flasks. Co^{60} radiation was delivered at a close rate of 2.3 Gy/min. Graded doses up to 36 Gy were given to generate survival curves.

Cimetidine, 1 mM, had no effect on growth of V79 monolayer cells. Exposure to 5 mM stopped growth by day 4. After removal of the drug on day 5, the cells began to divide again and eventually reached a plateau, which yielded numbers similar to control plates.

Spheroids, gassed as described above, had a resistant tail on the dose-survival curve. The addition of misonidazole, 1 mM, removed this tail, that is, sensitized the hypoxic cells. Cimetidine, 5 mM, also removed the resistant tail. When misonidazole, 2 mM, and cimetidine, 5 mM, were present at the same time, the resistant tail was removed but the overall sensitivity expressed by the final slope was not as great as with misonidazole alone. The experiment was repeated four times and showed the same result.

*Project 393.

**Experimental Oncologist, OCF London Regional Cancer Centre; and Professor of Radiation Oncology and Biophysics, University of Western Ontario, London.

In the present study, cimetidine had no effect, at 1 mM concentration, on the growth of V79 monolayer cell cultures or multicell spheroids compared to controls which did not receive radiation. However, at higher concentrations (5 mM), the growth of the cultures was arrested by the fourth day. Higher concentrations for short periods of exposure (5 hr) did not affect growth.

We conclude that cimetidine alters the effect of the hypoxic cell radiosensitizer, misonidazole, when tested using V79 multicell spheroids. It may explain the unexpected gastrointestinal symptoms noted in patients receiving the drug and abdominal radiation concurrently. Unlike potentiators it appears to be antagonistic, when combined with misonidazole, and is contraindicated in studies involving the radiation sensitizing chemical, misonidazole.

SURFACE ANTIGENS OF CULTURED HUMAN ASTROCYTOMAS: IDENTIFICATION AND INTERPRETATION OF SUBSETS*

J. G. CAIRNCROSS**, *London, Ontario*

When considered with morphology in culture and glial filament expression, cell-surface markers defined by mouse monoclonal antibodies provide a basis for subgrouping cultured human malignant astrocytomas.

The conclusion that the phenotypic differences among tumor subsets reflects their state of differentiation is based largely upon relationships between surface markers and glial-filament expression. Glial filament is an astrocyte-specific marker, absent in early astrocyte precursors, detectable in all mature astrocytes, absent in highly anaplastic astrocytomas and detectable in "well-differentiated" astrocytomas. In an effort to determine in a more direct way whether our surface markers are truly differentiation antigens, we studied their expression on mouse astrocyte lineages in culture. Although this work is incomplete, parallels have been found between the phenotypic characteristics of the normal cell (albeit murine) at selected points in its development, and those of certain cultured human astrocytomas.

The effects of culture conditions, differentiation promoters and tumor promoters on glial-filament expression and the cell-surface profile are under study. It remains to be seen whether in this solid tumor system it is feasible to construct a sophisticated immunopathological classification of astrocytomas on the basis of differentiation antigens, analogous to that of the hematopoietic and lymphoid malignancies.

*Project 471. (Final Report)

**Neuro-oncologist, OCF London Regional Cancer Centre; and Assistant Professor of Radiation Oncology, University of Western Ontario.

IN VIVO MODELS OF TUMOR GROWTH AND METASTASIS*

A. F. CHAMBERS**, *London, Ontario*

Tumor metastasis continues to be one of the most lethal aspects of cancer. We are studying the genetic properties of cancer cells with the aim of understanding how metastatic cells differ from cells that are non-metastatic. These studies use two distinct in vivo assays to model metastasis experimentally: 1) I.V. injection of tumor cells into chorioallantoic membrane veins of chicken embryos, which are naturally immunodeficient hosts¹; and 2) I.V. injection into normal, immunocompetent mice^{2,3}.

Using the chick-embryo model, we are investigating genes that may be responsible for metastatic properties of the tumor cells. In addition, we are examining the role that viral oncogenes play in the metastasis process. Using the mouse model, we are studying rapidly changing metastatic properties. The instability of the metastatic phenotype, which we have described, may call for new strategies in the treatment of metastatic disease.

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*RP-200.

**OCF Career Scientist, London Regional Cancer Centre.

ADDITIONAL INVESTIGATIONS

Dr. Haydn Bush, Director of the London Regional Cancer Centre, reports on the following clinical and basic research investigations:

EXPERIMENTAL ONCOLOGY

- Dr. J. F. Harris is employing immunology and somatic cell genetics to analyze the phenomenon of metastases. The objectives of this research are: To measure the effective rate of generation of metastatic liver colonizing variants of embryonal carcinoma (EC) cells; to develop new monoclonal antibodies and to use them to assess the functional significance of oncodevelopmental antigens expressed by metastatic variant EC cells; and to develop anti-idiotypic monoclonal antibodies against receptors on human natural-killer cells relevant to target-cell recognition. This work is supported by the National Cancer Institute of Canada.
- Dr. Ann F. Chambers is studying tumor progression and metastasis using an in vivo assay in the embryonic chick. To study experimental metastasis, she has developed a model system in which cell growth or death is monitored in the chick following I.V. injection. This assay is being used to determine which genes contribute to experimental metastatic ability. In addition, DNA from human tumor cells is being studied in the hope of describing previously unknown oncogenes, which contribute to metastatic growth in vivo. This work is supported by the National Cancer Institute of Canada.
- Dr. W. R. Inch, with Drs. Sharp and Peemoeller, is using two-dimensional nuclear magnetic resonance to monitor the relaxation parameters in normal, preneoplastic and neoplastic systems, to further clarify the potential of NMR in studies of cancer. This work is supported by a research grant from the Province of New Brunswick. Furthermore, Dr. Inch is studying the biology of hypoxic cells and the diffusion of cytotoxic drugs in multicell spheroids. This work is supported by Upjohn Company in Michigan.
- Dr. W. R. Inch, in association with Dr. Trevithick of the University of Western Ontario, is evaluating the production of cataract by ionizing radiation. This work is supported by the Medical Research Council.
- Dr. J. Koropatnick is carrying out studies on the amplification of the metallothionein-I gene in mouse liver during development and after treatment with cadmium. He will use the in vivo gene amplification model to assess the role of gene amplification in carcinogenesis. In addition, Dr. Koropatnick is using a plant lectin gene to identify developmentally regulated genes in chicken muscle and human placenta. Mammalian gene(s) will be used to assess changes in lectin DNA sequences and in RNA expression during cell transformation and in highly metastatic cell types.
- Dr. J. S. Gardner, a Terry Fox Fellow, continues her work in developing human-human hybridomas that have been established using lymphocytes from cancer patients with a human hybridoma cell line.

- Dr. J. D. Awde, a Terry Fox Fellow, is studying the use of hydroxyurea as a synchronizing agent before radiation and chemotherapy.
- Dr. J. G. Cairncross is continuing to analyze the effects of differentiation promoters on human astrocytomas, and also is producing mouse monoclonal antibodies to astrocyte differentiation antigens.
- Drs. W. I. Kocha and H. Bush continue work with their model for head and neck squamous-cell carcinoma, using DMBA-painted, golden-hamster cheek pouches. The distribution of cells within the cell cycle has been determined for golden-hamster bone marrow. Studies are being done to determine whether marrow protection will allow an increase in the doses of both phase-specific and non-phase-specific agents with consequent improved responses of tumors not so readily synchronized. Dr. J. D. Awde has established the baseline, cell-kinetic data and the preliminary pharmacologic data on high-dose hydroxyurea as a synchronizing agent.

RADIATION PHYSICS

- Dr. D. J. Dawson is applying ionometric and convolution techniques to evaluate electron fluence effects in the regions of inhomogeneities of varying electron density for photon beams of high energy. This work is supported by the Medical Research Council.
- Dr. D. J. Dawson and Mr. M. A. Gribble are evaluating quality assurance data from studies on both a Co-60 unit and linear accelerators.
- Since modifying the Selectron LDR remote brachytherapy unit applicators in 1982, Mr. M. A. Gribble has continued the evaluation of the new designs. Of the 65 Selectron insertions performed to date (November 1984), 57 have used the modified applicators, and only minor problems were encountered.

NUCLEAR MAGNETIC RESONANCE STUDIES

- Dr. J. Skilling continues to evaluate the role of NMR scanning in the assessment of abdominal disease in non-Hodgkin's lymphoma and Hodgkin's disease.
- With the arrival of the new NMR facility for metabolic research at Victoria Hospital, Dr. Levin will initiate forearm muscle studies to assess resting energy states, lactate and ATP production, and muscle mass in cachectic cancer patients. In addition, using previous *in vitro* data from these laboratories which demonstrated that the proton NMR relaxation time T1 of various tumors was significantly longer than values in normal tissues, Dr. Inch will study this phenomenon *in vivo* using the new NMR facility.

NEURO-ONCOLOGY

Drs. J. G. Cairncross and D. R. Macdonald are studying the timing of post-operative CT head scans which would permit the physician to differentiate post-surgical artefact from residual tumor. A Phase III study is underway in collaboration with Duke Uni-

versity, the University of Northern Carolina and Northwestern University; this will compare AZQ to BCNU following maximum feasible surgery and standardized radiotherapy. Nearing completion is Phase II study of adults with recurrent malignant glioma treated with high dose cis-platinum and adults with recurrent malignant glioma now are being entered into the NCIC trial using N-methylformamide (NMF).

CARCINOMA OF THE BREAST

The London-Hamilton Phase-III adjuvant protocol is underway using intensive, 12-week adjuvant chemotherapy versus standard 36 weeks of chemotherapy. This study is funded by MRC.

CARCINOMA OF THE BRONCHUS

Recently, Dr. W. I. Kocha analyzed the data from his Phase II study using cis-platinum with alternating vinblastine and bleomycin by continuous infusion in patients with non-small-cell carcinoma. This promising study is being followed by an adjuvant study in patients with resectable, primary, non-small-cell carcinoma of the bronchus. In addition, he will evaluate this pattern of chemotherapy in patients with localized unresectable disease to see whether this regimen makes surgical resection possible.

LYMPHOMAS

The lymphoma group continues to accrue patients in the NCIC-sponsored, Phase III study of escalated Bactrim/Septra in poor-prognosis, non-Hodgkin's lymphomas. These patients are participating in HD.4 study of advanced Hodgkin's disease. Dr. Skillings is study chairman for a new phased study of acivicin in relapsed, poor-prognosis lymphomas. Another study is being initiated using menogarol with relapsed nodular lymphoma. Pending is Phase II study of interferon for relapsed hematologic malignancy.

OVARIAN CANCER

Patients are being entered into NCIC-sponsored studies. In addition, Dr. Levin, working with Dr. Tustanoff, has begun a study to assess the efficacy of CA125 antigen as a tumor marker in ovarian cancer; particular attention is being paid to CA125 levels in patients with microscopic disease at the time of second-look laparotomy.

SARCOMAS

Recently, we have been joined by Dr. V. H. C. Bramwell, who is co-ordinator for the EORTC Sarcoma Group. Patients with soft-tissue sarcoma are being accrued into an adjuvant EORTC study. Also those with osteosarcoma are being entered into an EORTC-sponsored study to assess the tolerability and efficacy of Adriamycin

plus cis-platinum versus Adriamycin, cis-platinum and high-dose methotrexate in this disease. Patients with metastatic, soft-tissue sarcoma are being entered into an NCIC-sponsored study into the use of mitoxantrone hydrochloride.

MYELOMA

Dr. A. Cheung will evaluate the efficacy of half-body irradiation in patients with myeloma who have relapsed following chemotherapy.

ENDOMETRIAL CARCINOMA

Drs. Levin, Bush and Nisker will evaluate the efficacy of medroxyprogesterone as an adjuvant, following radiation, for patients with high-risk Stage I, Stage II and Stage III endometrial carcinoma.

DENTAL ONCOLOGY

Dr. J. D. Awde is conducting a study to compare Microstix-candida reagent strips with culture and sensitivity swabs. This is being funded by the Ames Division of Miles Laboratories. In addition, he will assess the efficacy of the troche form of clotrimazole in patients with oral candidiasis.

RADIATION ONCOLOGY RESEARCH

- Dr. A. Cheung will do a pilot study of fractionated, sequential, half-body irradiation in patients with multiple myeloma refractory to chemotherapy. Other proposed prospective clinical studies include primary radiotherapy for breast carcinoma after tumor excision, combined radiotherapy and chemotherapy for advanced cervical carcinoma, preoperative radiotherapy for colorectal carcinoma of borderline resectability, and a nutritional study on patients receiving pelvic radiotherapy.
- Dr. J. A. Hammond will evaluate the local control rate of carcinoma of the soft palate and tonsil by radiotherapy in the London Regional Cancer Centre.
- Drs. Bush, Dar and Tustanoff have begun on the prognostic and therapeutic significance of steroid receptors in breast carcinoma. Also, Dr. Dar proposes to study the local experience with uterine sarcomas, and mantle irradiation of patients with mediastinal involvement by Hodgkin's disease.
- Dr. P. Banerjee and Mr. M. Gribble completed a preliminary survey on the use of the after-loading Selectron units in the London Centre between 1982 and 1984. In October 1984, they presented the data and the local experience at a meeting of the Selectron Users' Committee in Innsbruck, Austria. Also, Drs. P. Banerjee and D. Dawson have undertaken to study the results obtained when medulloblastoma is treated by combined photon-beam irradiation of the cranium and electron scanning of the spinal axis.

University of Western Ontario, London

A COHORT STUDY OF THE EFFECT OF AGE AT FIRST FULL-TERM BIRTH UPON THE RISK OF DEATH FROM BREAST CANCER*

K.M. STAVRAKY^{*,} *London, Ontario*, M.E. SMITH[†], *Ottawa, Ontario*

A.E. DONNER[‡], *London, Ontario*

J.R. MILLER[§] and S.H. UH^{||}, *Vancouver, B.C.*

The increasing risk of breast cancer with increasing age at which a woman bears her first full-term child was clearly shown in an international collaborative study carried out in seven different centres^{1,2}. This study estimated that women who bear their first child under the age of 18 have about one-third the risk of breast cancer than those whose first child was born at the age of 35 or later. The investigations that formed the international study were all case-control interview studies, which attempted to identify all cases of breast cancer in the defined areas; controls were patients hospitalized for diseases other than breast cancer in the same hospital as the cases.

However, several recent case-control studies have shown that the relationship was not consistent and, for this reason, we have undertaken a large cohort study. In this study, women who bore their first child in British Columbia between the years 1950 and 1973 were identified and grouped according to their ages at the time of first birth. Record-linkage techniques identified all deaths among these women, which occurred in British Columbia. Among 273,284 women whose records of first birth were entered into the study, we identified 2571 deaths from all causes, of which 215 were due to breast cancer. The majority of these deaths (79%) occurred before the age of 50, and 94% of the deaths were before age 55. Analysis of the data provided no evidence that age at first birth increased the risk of death from breast cancer. We have not identified any defect in data collection or analysis, which would have obscured a real relationship between breast cancer mortality and age at first birth. Thus we conclude that late first birth did not increase the risk of breast cancer occurring before the age of 55.

*Project 333.

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THE EFFECT OF SOCIOECONOMIC STATUS ON THE PROGNOSIS OF CANCER OF VARIOUS SITES*

K.M. STAVRAKY**, *London, Ontario and*

J.E. KINCADE†, *Chapel Hill, NC., USA*

The purpose of this study is to determine whether socioeconomic status (SES) has an effect on the prognosis of cancer of several sites, especially breast, lung, large bowel, endometrium, cervix, skin (melanoma), and the lymphatic system (lymphomas). In particular, we are testing the hypothesis that cancer has poorer prognosis (high recurrency rates or low survival rates) among persons of low SES than among persons of high SES, even when other important factors such as stage of disease and method of treatment are the same.

Interviewing, collection of one year, follow-up information on all patients interviewed and data processing have been completed and data analysis has begun. At present we are analyzing data for the two most frequent sites at the OCTRF London and Hamilton Regional Cancer Centres — breast and lung. Since education is our principal measure of SES, we have begun by dividing the breast and lung cancer patients at each clinic into three educational groups, high (grade 12, 13 or more), medium (grades 10, 11), and low (grade 9 or less). We will then compare the survival rates and recurrence rates in the three groups, adjusting in our analysis for other factors which may affect prognosis — stage of disease, pathologic grade, treatment, presence of other chronic illness — to determine whether SES independently affects prognosis.

*Project 420.

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Ottawa Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. G. E. Catton, Director of the Ottawa Regional Cancer Centre, reports on the following clinical research investigations:

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT

Investigators continue contributing patients to the NSABP protocols to determine the effect of adjuvant chemotherapy and hormonal therapy in breast cancer patients according to the age of the patient, stage and estrogen and progesterone status.

Accrual is also open to NSABP colon study evaluating the postoperative portal vein infusion of 5-FU and sodium heparin.

NATIONAL CANCER INSTITUTE OF CANADA

The Ottawa group participates in many of the national trials including several from the Investigational New Drug Program.

- Chemotherapy and hormonotherapy in the treatment of Stage II breast cancer in postmenopausal patients.
- Treatment of limited and extensive small cell carcinoma of the lung.
- MOPP/ABV hybrid versus MOPP/ABVD for advanced or recurrent Hodgkin's disease.
- Treatment of poor prognosis of non-Hodgkin's lymphoma.
- Etidronate disodium versus placebo in the treatment of multiple myeloma.
- Lomidamine in the treatment of advanced breast cancer.
- Interferon in advanced renal cell carcinoma.
- Mitoxantrone in the treatment of soft tissue sarcomas.
- CBDCA in the treatment of advanced ovarian carcinoma.

ONTARIO CO-OPERATIVE ONCOLOGY GROUP

Drs. J. Devitt and R. McDermot are contributing patients to a trial to assess, in node-negative patients, the effectiveness of breast radiation following partial mastectomy and axillary dissection to carcinoma of the breast.

DRUG-COMPANY-SPONSORED TRIALS

- A comparison of the standard combination of cyclophosphamide, Adriamycin and 5-FU to cyclophosphamide, Novantrone and 5-FU as first-line treatment for metastatic breast carcinoma.
- Tamoxifen versus Megace in the treatment of metastatic breast carcinoma in

postmenopausal patients.

- Flutamide in the treatment of advanced prostatic carcinoma.
- Megace plus low-dose stilbestrol versus stilbestrol alone in the treatment of advanced prostatic carcinoma.
- Interferon plus DTIC in the treatment of malignant melanoma.
- Phase I study of Adriamycin plus mitoxantrone in adenocarcinoma of the breast.
- Novantrone in surgically resected astrocytomas.

LOCAL STUDIES

- Cis-platin plus cytosine arabinoside in the treatment of head and neck carcinoma.
- Intrathecal methotrexate, cytosine arabinoside, hydrocortisone plus thio-TEPA for meningeal involvement by malignancies.
- Intra-arterial cis-platin with and without disulfiram for localized bladder cancer.
- Double blind trial of Vitamins E and C versus placebo as protectors against doxorubicin cardiotoxicity.
- Transitional cell bladder carcinoma — intra-arterial platinum/radiotherapy/cystectomy.
- Lonidamine plus radiotherapy in the treatment of non-small cell lung cancer.
- Adjuvant, fractionated upper half-body radiation in the treatment of non-small cell lung cancer.
- Treatment of metastatic colorectal cancer with 24-hour infusion chemotherapy with sequential methotrexate, 5-FU and leucovorin rescue.
- A study of 5-FU plus mitomycin C in addition to irradiation in advanced carcinoma of the larynx and hypopharynx.
- Indomethacin and radiation mucositis in patients with epithelial ENT malignancies.
- Phase I study of riboxamide in all types of solid tumors and lymphoma. This trial also includes pharmacokinetic studies.
- Pain control — A pilot study to define and compare the pharmacokinetics of two morphine formulations.
- Phase I-II evaluation of intracarotid infusion of mitomycin C including pharmacokinetic studies.
- Adriamycin plus metronidazole in head and neck cancer.
- Intracarotid infusion of BCNU, cis-platin, VM-26 for intracerebral tumors, including pharmacology studies.
- Phase I-II study of combined intra-arterial and systemic chemotherapy for patients with glioblastoma multiforme and recurrent low grade gliomas and brain metastases.
- Oral tolerance of cyclophosphamide product prototypes with emphasis on gastrointestinal toxicity.

Hospital for Sick Children, Toronto**INTERMEDIATE FILAMENT PROTEINS AS MARKERS
IN PEDIATRIC MALIGNANCIES***

R. BAUMAL**, M.J. PHILLIPS†, C.R. SMITH‡ and
H. YEGER§, *Toronto, Ontario*

Undifferentiated pediatric and adult tumors have been studied by immunofluorescence and immunoperoxidase staining techniques, using antibodies to intermediate filament proteins — cytokeratins, vimentin, desmin, neurofilaments and glial fibrillary acidic proteins. In addition, we have used antibody against S100 protein, which is present in astrocytes of the central nervous system, Schwann cells of the peripheral nervous system and various other cell types including Langerhan's and nevus cells of the skin. On the basis of their staining with these various antibodies, tumors usually could be identified as having arisen from epithelium, mesenchyme, muscle, neurons or glial cells. Epithelial neoplasms stained for cytokeratins; tumors of mesenchymal or lymphoid origin were positive for vimentin; tumors derived from muscle were positive for desmin; and tumors derived from neurons and glial cells were positive for neurofilaments and GFAP or S100 protein respectively. These antibodies proved to be extremely useful in the diagnosis of various neoplasms, especially those that were undifferentiated and difficult to diagnose only on the basis of light and electron microscopy.

*Project 463.

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**Ontario Cancer Institute incorporating the
Princess Margaret Hospital, Toronto**

**LEUKEMIA PROGRAM
AT THE ONTARIO CANCER INSTITUTE***

E. A. McCULLOCH** and J. E. CURTIS†, *Toronto, Ontario*

The leukemia program at the Ontario Cancer Institute is a collaboration between clinical and laboratory scientists; its objective is to define cellular or molecular characteristics of leukemic cells and to use this information as the basis for therapeutic innovation.

The clinical strategy is based upon sequential therapeutic trials. A fourth such trial, now underway, consists of the use of cytosine arabinoside (Ara-C) both for remission induction and maintenance. The protocol is as follows: 3 g/M² of Ara-C (reduced to 2 g/M² for patients 60 years of age or over) twice daily for six days. Prednisone (40 mg/M²) is given to reduce toxicity. Patients entering remission are maintained with Ara-C, 100 mg/M² by continuous infusion daily for five days at monthly intervals. Twenty-seven patients have now been entered into the protocol. Fifteen complete and four partial remissions have been achieved — a response rate of 70%. This compares favorably with the 55% response rate achieved using Adriamycin, Ara-C and thioguanine in the previous trial. However, in order to achieve significance, at least 40 patients must be entered into the trial.

The program employs a clonogenic assay of blast progenitors developed in this laboratory. Three culture indices are obtained at presentation and relapse. First, blast colonies are subcultured to obtain the secondary plating efficiency (PE2) — a measurement that has been shown to be highly correlated with successful remission induction. Second, Ara-C is added to cultures in increasing concentrations in order to construct survival curves. Third, colonies surviving exposure to Ara-C are replated; using the PE2 values from untreated cultures to normalize the results, a dose-response curve can be constructed for the effect of Ara-C on blast renewal. In practice, blast renewal was found to be either sensitive or resistant to the drug.

*Project 402.

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A preliminary analysis of the laboratory data shows that the PE2 value continues to be a powerful attribute contributing to outcome ($p = .003$ for 25 AML patients). Further, no patient with a PE2 of less than 40 colonies/ 10^4 cells failed to achieve remission. This observation differs from our previous experience, where failures were sometimes observed in patients whose blasts renewed poorly. A correlation between response and treatment and blast sensitivity to Ara-C was not seen. However, an association is emerging between sensitivity to Ara-C of the self-renewal capacity, and successful remission induction. The effect appears to be most important for patients with high PE2 values; we have achieved remissions in this group only when PE2 was sensitive to Ara-C. It should be emphasized, however, that these observations are preliminary; as in the assessment of the clinical effect of the drug, more patients are needed to evaluate the significance of laboratory findings.

The culture assay for colony formation by blast progenitors has important limitations. For example, it cannot be used to evaluate the effect of continuous exposure to drugs over long time periods. We have developed a new procedure that avoids some of these limitations. Blast cells were cultured in suspension in the presence of media conditioned by normal leukocytes stimulated by phytohemagglutinin (PHA-LCM). Under these conditions, the number of clonogenic blast progenitors increased for seven days; the secondary plating efficiencies of these progenitors increased or remained stable.

Blasts grown in suspension culture can be recultured repeatedly. The procedure is to harvest the cultures on day 7, wash and resuspend at a cell density of 10^6 cells/ml. With this regimen, in some patients, exponential growth of blast progenitors has been observed for as long as 50 days with a cumulative increase of more than three decades. This new system shows promise as a model for leukemic progenitors growing *in vivo*.

Other lines of investigation continue, we use monoclonal or heteroantisera to determine the phenotypes of AML blasts. In about 30% of patients, blasts can be identified which bear markers usually associated with different lineages. This phenotype has been termed "lineage infidelity". In our initial studies we observed an association between lineage infidelity and poor prognosis. Similar observations have been made on patients studied over the last year.

CLASSIFICATION OF SURVIVAL CURVES*

A. CIAMPI**, Toronto, Ontario

We have continued our development of statistical methods and computer software for the analysis of survival curves, within a framework that emphasizes statistical rigor, exploratory flexibility, and communicability of results in direct clinical language. Our program includes two components: Classification and regression.

Classification

We have worked on an improved version of recursive partition for identifying and describing prognostic groups¹. A related development is that of a clustering method known as amalgamation², the object of which is to cluster populations of patients with censored survival times.

Regression

We have developed both parametric and semiparametric methods.

Parametric Methods. We have completed the study of log-gamma regression³ and extended it to the case in which the error term is the logarithm of an F distribution. A program has been written, which simultaneously estimates (by maximum likelihood methods) both baseline survival function and covariate effects.

Semiparametric Methods. Continuing our work on the extension of the Cox model⁴, we have defined a new model, which includes both Cox and accelerated failure time regressions as particular cases. These developments will be useful especially in oncology, because they allow the analyst to deal correctly with crossing survival curves and with other situations characterized by time-varying relative risks.

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*Project 426. (Final Report)

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CLINICAL TRIALS SECRETARY FOR GASTROINTESTINAL TUMOR GROUP*

B. J. CUMMINGS** and G. DeBOER†, *Toronto, Ontario*

This project provides secretarial assistance for studies on patients with gastrointestinal malignancy.

The benefits and toxicity of combined treatment with 5-fluorouracil, mitomycin C and radiation are being studied in patients with anal canal and perianal carcinomas¹. Primary tumor control rates have improved from 60% with radiation alone to 90%. Current studies are comparing different radiation fractionation schedules.

Matched pairing of patients with squamous-cell carcinoma of the esophagus treated by radiation alone, and by radiation plus 5-fluorouracil, has shown that combined modality treatment improves local control at one year from c.30% to c.60%.

A retrospective review of patients with colon cancer who had received post-operative total abdominal irradiation was completed², and a randomized trial comparing this adjuvant therapy with surgical resection alone has been opened. A pilot study of preoperative radiation for rectal adenocarcinoma is nearing completion, and a randomized trial is planned.

A randomized trial comparing 5-fluorouracil with 5-fluorouracil plus folinic acid has been commenced for patients with metastatic colorectal carcinoma.

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*Project 427.

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CLINICAL TRIALS IN BREAST CANCER*

R. M. CLARK**, N. F. BOYD†, U. AMBUS‡ and K. I. PRITCHARD§

Toronto, Ontario

Four randomized controlled clinical trials are now in progress.

These are:

1. A randomized controlled trial of ovarian irradiation and prednisone, following operation and radiotherapy, was undertaken for carcinoma of the breast. This trial compared three forms of adjuvant therapy: ovarian irradiation and prednisone; ovarian irradiation alone; and no further treatment. There have been 756 patients enrolled and they now have been followed for at least eight years. In premenopausal women, aged 45 years or more, ovarian irradiation and prednisone significantly delayed recurrence, and prolonged survival. Further follow-up and analysis continue.
2. A randomized controlled trial of postoperative treatment of breast cancer is being conducted in premenopausal patients with histologically involved axillary nodes. This trial compares two treatment modalities: (a) combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and ovarian irradiation plus prednisone; and (b) CMF alone. The trial is designed to determine if chemotherapy and hormonal therapy are complementary. To date 193 patients have been enrolled. As yet no results are available.
3. A randomized controlled trial of postoperative treatment of breast cancer is being conducted in postmenopausal patients with histologically involved axillary nodes. No adjuvant therapy is known to benefit this group of patients and this trial examines the usefulness of tamoxifen as an adjuvant agent. To date, 403 patients have been enrolled. Overall the four-year, actuarial, relapse-free rates were 48% for patients receiving tamoxifen vs 35% for patients receiving no further treatment. As yet, there is no difference in overall survival between these two groups of patients. Estrogen receptor status was known in 250 patients and progesterone receptor status in 241. Improvement in disease-free survival at present appears to be confined to the receptor-positive subgroup. These early results

*Project 446, including Projects 378 and 386.

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suggest that tamoxifen is useful in decreasing the recurrence rate in postmenopausal women with axillary-node-positive breast cancer following mastectomy because benefit appears to be confined to women with receptor-positive breast cancer.

4. In a Phase II trial, the value of tamoxifen in the treatment of metastatic breast cancer in premenopausal women is being studied. Of 53 evaluable patients, 4 have had complete responses (CR) and 10 have had partial responses (PR). Six patients have remained stable (ST) on treatment. The response rate (26% for CR + PR; 38% for CR + PR + ST) and the response duration (13+ months) seen in this study suggests that tamoxifen may achieve an effect comparable to that of ovarian ablation in premenopausal women with metastatic breast cancer. The study has also shown that steroid receptors generally were predictive of response to tamoxifen, and that tamoxifen response was highly predictive of response to subsequent ovarian ablation.

A PHASE III CLINICAL TRIAL OF MISONIDAZOLE AND RADIATION THERAPY*

G. M. THOMAS**, *Toronto, Ontario*

The purpose of this randomized Phase III clinical trial is to determine whether, in patients with advanced carcinoma of the cervix, the addition (to pelvic irradiation) of the hypoxic cell, radiosensitizer misonidazole can improve pelvic control and survival rates. A previous Phase I study had determined that misonidazole could be given safely on 22 radiation-treatment days in a dose of 0.45 g/M². Patients were therefore randomized in a double-blind fashion to receive this dose of misonidazole, or placebo, for hours before pelvic irradiation.

To date, 67 patients have been randomized to the study. A minimum follow-up period of three years is required after treatment before one can assess survival rates. The patients will be followed until outcome data is available.

*Project 448.

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INVESTIGATION OF A STEM-CELL MODEL OF HUMAN TUMOR GROWTH*

R. N. BUICK**, A. CIAMPI† and J. E. TILL‡, *Toronto, Ontario*

We have investigated the possibility that human tumors have a cellular organization based on stem-cell renewal differentiation.

We constructed mathematical models to aid in the analysis of stem-cell concepts in neoplasia. Initially a simple, deterministic stem-cell model was used to clarify the biological principles underlying the use of tumor clonogenic assays as predictors of clinical outcome^{1,2}.

We have extended these studies to include stochastic considerations (Ciampi, Buick and Till, in preparation). The main extensions of the earlier model have been to treat the proliferation of the cell population as a Galton-Watson branching process in which stochastic fluctuations lead to probability distributions in the numbers of each cell type around the mean values obtained from the earlier deterministic model. Another change has been to relax the hypothesis that cell division occurs at the same time for cells of the same age, after a fixed generation time. Clearly this assumption has no biological relevance. Instead, the modified model allows for the possibility of cell division at different times among various subpopulations of cells.

These modifications permit an estimate to be made of P_{sr} , the probability of self-renewal of tumor stem cells, under conditions where P_{sr} may take any value between zero and unity, i.e. where it need not be assumed that the tumor cell population contains any true stem cells capable of further self-renewal.

To test the usefulness of the model for analyses of experimental data, we have used the sample means and variances from experimental distributions of colony sizes from cultured ovarian tumor cells as an initial basis for estimating some key parameters of the model. These estimated parameters have been used as a starting point for simulations designed to generate distributions of colony and cluster sizes expected from the model for various specified values of the parameters. Comparisons of the experimental and simulated size distributions provide a preliminary test of the goodness of fit of the simulated distributions to the experimental ones. Simulations have also been used to test the sensitivity (of the colony and cluster size distributions) to changes in the value of some of the key parameters. Of particular interest is the probability of self-renewal of tumor stem cells, which may be the most

*Project 465.

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important single index of curability (potential for regeneration) of a tumor cell population.

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Toronto-Bayview Regional Cancer Centre

**CHARACTERIZATION OF CULTURE-INDUCED CYTOTOXICITY (CIC)
AMONG NATURAL KILLER CELL-DEPLETED, HUMAN PERIPHERAL
BLOOD LYMPHOCYTE SUBPOPULATIONS***J.J. RUSTHOVEN** and D. OSOBA†, *Toronto, Ontario*

Natural killer cells (NKC) cytotoxicity in human peripheral blood is mediated largely by lower-density lymphoid cells, which kill a variety of tumor-cell lines. Though these cells require no in vitro stimulation to mediate their cytotoxic effect, other lymphoid cells generate cytotoxicity against a similar range of tumor cell lines but only after in vitro culture.

Previously we had observed the generation of culture-induced cytotoxicity (CIC) from human peripheral blood lymphocyte subpopulations separated on a Percoll density gradient. This cytotoxicity is induced in short-term, fetal-calf serum-containing cultures and occurs among higher-density, NKC-depleted lymphoid subpopulations. Using a panning technique, we have characterized partially the cells responsible for this activity. Unlike most natural killer cells which stain with the monoclonal antibodies HNK-1⁺ and OKM1⁺ but not OKT3⁻, higher-density lymphoid cells, which generate CIC, were phenotypically HNK-1⁻ OKM1⁺ OKT3⁻. Only removal of OKM1⁺ cells before culture blocked the generation of CIC, suggesting that CIC precursor cells have a similar phenotype. In addition, we found that three teratocarcinoma cell lines were relatively resistant to natural killer cells but that two of the three were sensitive to cells mediating CIC.

At present we are working to define the mechanism of resistance of the insensitive teratocarcinoma cell line, and testing the effects of exogenous interleukin 2 on the generation of CIC.

*Project 468.

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ADDITIONAL INVESTIGATIONS

Dr. R. D. T. Jenkin, Director of the Toronto-Bayview Regional Cancer Centre, reports on the following clinical research investigations:

COMBINATION CHEMOTHERAPY IN NON-SMALL-CELL LUNG CANCER

Dr. David Osoba is conducting Phase II clinical trials to determine the value of bleomycin, cis-platinum and etoposide (VP-16) in non-small-cell lung cancer. In the first study, 53 patients with recurrent or extensive disease received these drugs and had an overall response rate of 45%. The response rate in the squamous and large-cell subtypes is 55% and for adenocarcinoma 20%. It is too early to determine whether this approach improves survival. In the second study, patients with "limited" squamous-cell carcinoma receive up to two cycles of treatment with bleomycin, cis-platinum and etoposide followed by radiation. The object of this study is to determine the response rate to chemotherapy in previously untreated squamous-cell lung cancer and to discover combined modality therapy associated with unexpected or increased toxicity.

INTRAPERITONEAL CHEMOTHERAPY FOR OVARIAN AND COLORECTAL CANCER

Dr. I. J. Kerr has initiated two clinical-pharmacologic studies using high-volume intraperitoneal chemotherapy in selected patients with intra-abdominal metastatic ovarian and colorectal carcinoma. Drugs being studied include aclarubicin (Phase I) and 5-FU (Phase II).

EFFECT OF PATIENT AGE ON THE CLINICAL PHARMACOLOGY OF ANTICANCER DRUGS

Dr. I. G. Kerr has initiated a study looking at the relationship between patient age (particularly the elderly) with toxicity and pharmacokinetics of selected anticancer drugs. Initial drugs to be studied would include 5-FU, Adriamycin and vincristine.

AMBULATORY INFUSION PUMP PROGRAM

Drs. I. G. Kerr and N. Iscoe have begun to develop an ambulatory infusion pump program for future Phase I-II drug trials. Initial studies will investigate use of 5-FU and FUDR in patients with metastatic colorectal cancer.

MELANOMA

Dr. N. Iscoe has reviewed 198 patients with malignant melanoma to assess the value of diagnostic and staging investigations in the initial examination and follow-up of this disease. The data, which have been combined with similar information from the

Princess Margaret Hospital, indicate that physical examination is the most sensitive method of detecting metastatic melanoma.

NATURAL KILLER CELLS

Natural killer cells may play an important role in the body's defences against cancer. Dr. J. J. Rusthoven is studying the mechanisms by which the destruction of tumor cells by natural killer cells is altered during culture. This study may lead to clinically useful improvements in the eradication of tumor cells by the patient's own natural killer cells.

PSYCHOSOCIAL ASPECTS OF CANCER

The Psychosocial Research Group is developing a questionnaire and has commenced a longitudinal study to determine if the questionnaire and disease-related factors can predict future anxiety and depression in patients with cancer.

BREAST CANCER

Dr. D. J. A. Sutherland continues his analysis of steroid receptor assays and clinical correlates in patients with breast cancer. Several collaborative clinical studies in breast cancer are in progress. In addition, investigations are being pursued on the influence of several endocrinopathies on sex-hormone-binding globulin.

CO-OPERATIVE CLINICAL TRIALS

Patients are being entered into several U of T and NCIC clinical trials: melanoma, small-cell lung cancer, non-Hodgkin's lymphoma, mesothelioma and control of chemotherapy-induced nausea and vomiting. Other trials include combined modality therapy in advanced head and neck cancer, and bisantrene in hypernephroma.

EWING'S SARCOMA

Dr. M. P. Berry has reviewed the recent experience in Toronto with this tumor, particularly with regard to a pilot study of the addition to adjuvant chemotherapy of sequential half-body radiation.

EFFECTS OF NITROAROMATIC RADIOSENSITIZERS ON RADIOLYTIC OXYGEN DEPLETION IN MAMMALIAN CELLS AND IN AQUEOUS SOLUTION

Dr. H. B. Michaels is developing a radiation-chemical model to elucidate the mechanism for the complex inter-related processes of radiolytic oxygen depletion and the reduction chemistry of nitroimidazoles at low concentrations of oxygen. The radiation-sensitizing drugs — misonidazole and metronidazole — interfere with radiation-chemical oxygen depletion and protect oxygen from depletion in mammalian cells irradiated at ultra-high dose rates, in addition to their action as radiosensitizers of hypoxic cells. Parallel experiments in aqueous solutions of sensitizers are in progress.

PHYSICS MEASUREMENTS ON THE THERAC-25 LINEAR ACCELERATOR

Mr. P. F. O'Brien and the clinical physics staff are continuing studies of the radiation-beam characteristics of the photon and electron modes of the new Therac-25. Mr. O'Brien and Dr. Michaels have undertaken radiation protection studies on the Therac-25, specifically measuring the transmission of neutrons through concrete, wood and polyethylene. The data were used to design a new shielding door for the Therac-25 room.

DEVELOPMENT OF A MICROCOMPUTER-ASSISTED, PATIENT-CONTOUR-TAKING DEVICE AND COMPENSATOR DESIGNING APPARATUS

The clinical physics staff have designed a system, presently being constructed in the machine shop and electronic shop, which will enable the physicist or dosimetrist planning radiotherapy to obtain information about patient contours quickly and accurately. The apparatus consists of sensors to identify position co-ordinates on the patient's skin, which then are processed by a microcomputer to display the contour. The information is coded in digital form and can be used in the design of tissue compensators for radiotherapy.

BRACHYTHERAPY DOSIMETRY

Dr. R. A. Siwek and Mr. P. F. O'Brien are carrying out brachytherapy dosimetry on the Selectron remote afterloading unit (for radioactive implants) using the Fletcher-type applicators; their ultimate aim is to verify the distribution of radiation when active spheres of caesium-137 are placed in the uterus and cervix.

University of Toronto

HORMONAL CONTROL OF PROSTATIC CANCER*

B. G. MOBBS**, *Toronto, Ontario*

The R3327 prostatic adenocarcinoma, which arose spontaneously in the dorsolateral prostate of an aged Copenhagen rat in 1961¹, has many of the characteristics of human prostatic carcinoma, and has been widely used as a model for the human disease. It has a similar enzyme profile, contains androgen receptor (AR) and cytosolic estrogen receptor (ER), and growth can be retarded by androgen deprivation brought about by castration or estrogen treatment. However, as a fraction of the cell population is not androgen-sensitive, the tumor eventually escapes from hormonal control and resumes its growth².

In this laboratory, we are investigating changes in the concentration of receptor proteins for androgen, estrogen and progestins in the R3327 tumor brought about by treatment of the host animals with diethylstilbestrol (DES) — a standard treatment for advanced prostatic carcinoma in man.

Changes in AR distribution between subcellular fractions were consistent with androgen deprivation. Nuclear AR concentrations were reduced from approximately 50% to approximately 15% of the total cellular AR, the concentration of cytosol AR was correspondingly increased, and the proportion of cytosol AR, which was occupied by endogenous androgen, was decreased. No significant changes in the total cell AR content were observed within the time of treatment (20 days). Estrogen receptor was undetectable in the nuclear fraction of untreated tumors, and could be demonstrated in low concentrations in only one-fifth of the treated tumors. However, cytosol progesterone receptor (PgR), the synthesis of which is stimulated by estrogen in female estrogen target organs, was detected in low concentrations ($<20 \times 10^{-15}$ mole per mg cytosol protein) in untreated tumors, and was present at up to six times this concentration in treated tumors. The concentration of cytosol PgR correlated strongly with the amount of DES ingested during the treatment period. This observation supports the concept that prostatic carcinoma is a potential target for direct estrogenic and progestogenic action.

*Project 251.

**Associate Professor of Surgery (Research), University of Toronto.

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2. Isaacs JT, Heston WDW, Weissman RM, Coffey DS: Animal models of the hormone-sensitive and -insensitive prostatic carcinomas, Dunning R-3327-H, R-3327-HI, and R-3327-AT. *Cancer Res* 1978; **38**: 4353.

THE IRRADIATED LARYNX AND VOICE*

M. L. STOICHEFF**, *Toronto, Ontario*

The preservation of the voice-producing mechanism is important in the management of laryngeal cancer by radiotherapy. Although centres involved in the radiation of glottic cancer must be concerned with the effective control of cancer and with patient survival and complication rates, it is also important to determine how specific techniques affect the quality of the output of the preserved larynx. Voice quality contributes to the quality of life of the irradiated individual.

Published reports suggest that about 75-80% of irradiated patients with successfully treated, noninfiltrative vocal-fold cancers will have a normal voice. Self ratings of vocal results following radiotherapy also have been reported. Questionnaires completed by 227 patients 4-15 years following treatment for glottic cancer at the Princess Margaret Hospital, Toronto, revealed that most of them (83%) had normal to near normal voice.

To date no study has compared the voices of irradiated patients with those of normal population. The present study elicited information about the perceived voice quality of glottic cancer patients who received 5000 rads in 20 treatments over a period of four weeks.

The subjects for this study were 46 men with glottic cancer, all of whom had no demonstrable recurrence one year after cessation of radiotherapy at the Princess Margaret Hospital. All patients received 5000 rads in 20 treatments over a period of four weeks. The age distribution of the cancer patients approximately 12 months was 39-82 years. The control subjects were 58 men with no history of laryngeal problems or dysphonia. They were selected because they had voices representative of the voices of individuals in their age range. Their age distribution was 47 to 83 years.

Following specific radiotherapy the voices of patients with laryngeal cancer were subjected to perceptual evaluation. Interval scaling of the severity of perceived dysphonia was completed for the voices of male patients sampled before and one year after radiation and for a set of male controls. Eight listeners did this quantitative rating and also specified the predominant quality in each voice. The results indicated that the pretreatment group had the highest degree of dysphonia. Radiotherapy decreased this dysphonia but not to the point that post-treatment voices were indistinguishable from those of normal subjects. Also, the voice qualities of laryngeal cancer patients shifted toward those of the control group after radiotherapy; over one-half of the irradiated patients were judged to have voices with rough or normal qualities.

*Project 323. (Final Report)

**Professor of Speech Pathology, University of Toronto.

CONSTRUCTION AND TESTING OF CODED-APERTURE COLLIMATION SYSTEM FOR GAMMA-RAY CAMERAS*

M. L. G. JOY**, *Toronto, Ontario*

The purpose of this research was to construct and test a novel, relatively inexpensive, tomographic imaging system for use in nuclear medicine, namely the Fourier multiaperture emission tomography (FMET)¹. Physically the FMET device, which is mounted on a gamma camera like a regular collimator, allows the positioning of 32 coded-aperture plates in front of the camera. The coded images so produced are digitally processed to form a series of tomographic "slices" in planes parallel to the camera. The thickness of these slices increases with depth but is about 1.6 cm to 10 cm from the plate. The resolution in the plane is about 8 mm. Currently, the time required for the acquisition of the coded images is from 10 to 20 minutes. Processing time has been reduced to 45 sec per slice.

This project is complete. We have measured the noise performance of the FMET system and compared with theory². The results of this comparison suggest that this theory accurately predicts the statistical performance of FMET. In addition to this work, we have tested a modification to this method which gives a 35% improvement in the deviation of quantum noise.

With respect to the potential usefulness of this technique it appears that the potential benefits of its tomographic capability are outweighed by the high quantum noise observed in practice. The root of the problem is the high counting rates associated with the largely open FMET apertures. Therefore the technique is limited to situations in which one wishes to image small amounts (200 μ Ci) of activity.

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*Project 413. (Final Report)

**Associate Professor, Institute of Biomedical Engineering and Department of Electrical Engineering, University of Toronto.

A RESEARCH PROGRAM IN ADULT LEUKEMIAS*M. A. BAKER**, *Toronto, Ontario*

We have continued studies of the membrane properties of leukemic cells from patients with acute myeloblastic and chronic myelogenous leukemia.

Human leukemic myeloblasts shed glycoproteins from the cell surface during short-term, in vitro culture. Shed surface glycoproteins yield a characteristic profile when studied by gel chromatography, isoelectric focusing, immune precipitation, and polyacrylamide gel electrophoresis. Isolation of immunologically active material yields a compound of approximately 75,000-80,000 daltons, with an isoelectric point of pI 7.6 to 7.9. Various morphological subtypes of acute myelogenous leukemia shed these compounds, but they are obtained most easily from the more differentiated M1 type. The shed compounds appear to be quantitatively and qualitatively different from compounds shed by other leukemic cells or nonleukemic cells.

Peripheral blood granulocytes from patients with chronic myelogenous leukemia (CML) were studied for accessibility of membrane sialic acid and galactose residues to sodium borohydride- ^3H radiolabelling after oxidation with sodium metaperiodate (PI/ B^3H) or with galactose oxidase (GO/ B^3H_4). Granulocytes from untreated patients with chronic myelogenous leukemia showed increased radiolabelling with PI/ B^3H_4 and decreased labelling with GO/ B^3H_4 when compared to normal granulocytes. Granulocytes from leukemic patients receiving chemotherapy showed normal labelling patterns. Gel electrophoresis of membrane extracts showed that the changes in PI/ B^3H_4 reactivity of CML cells were distributed over all membrane protein bands. Our data suggest that CML granulocyte membrane proteins are sialylated aberrantly with decreased accessibility of galactose residues, and that these changes may be reversed by drug treatment.

*Project RP-100.

**OCF Research Associate; Director, Oncology Program, Toronto General Hospital; and Professor of Medicine, University of Toronto.



Windsor Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. G. K. Mok, Acting Director of the Windsor Regional Cancer Centre, reports on the following clinical research investigations:

ADVANCED BREAST CANCER

The Windsor Regional Cancer Centre, in co-operation with Lederle Corp., is conducting a randomized trial comparing the effectiveness of single-agent Novantrone (DHAD) to standard CMF chemotherapy as first-line treatment in relapsing breast cancer. This is a crossover trial: includes both positive- and negative-estrogen receptor tumors, but excludes patients with liver metastases. This trial correlates with a similar trial in Australia.

SOUTHWEST ONCOLOGY GROUP

The Southwest Oncology Group (SWOG) is a large, multi-institutional co-operative study organization devoted to improving the understanding and treatment of neoplasms. Through the participation of physicians and scientists from many disciplines, the group embraces single and combined cancer trials including supportive care.

The Windsor Regional Cancer Centre, as an associate member through Wayne State University, has supported actively the SWOG program both in patient entry into protocols, and as active participants in brain and gastrointestinal committees. By this means, promising new agents and treatment modalities are introduced to upgrade the skills and services available in the Windsor area. An overlooked but superior advantage of membership is the high degree of discipline in clinical practice which these studies require. The principal investigators at this centre are Drs. D. B. McDonald, H. T. Abu-Zahra and S. S. Yoshida.

This centre will continue the active involvement with SWOG.



EPIDEMIOLOGY AND STATISTICS



CANCER INCIDENCE, MORTALITY AND TREATMENT IN ONTARIO

E. A. CLARKE, M.B., B.S., M.Sc.* N. KREIGER, M.P.H., Ph.D.**

L. D. MARRETT, Ph.D.** and C. L. SOSKOLNE, Ph.D.**

Toronto, Ontario

The Division of Epidemiology and Statistics is responsible for one of the mandates of the Foundation under The Cancer Act: the adequate reporting of cases and the recording and compilation of data. In pursuit of these objectives, the Foundation has maintained and improved a uniform case recording system adopted by the regional cancer centres in 1947 and the Princess Margaret Hospital, incorporating the Ontario Cancer Institute, since it was founded in 1957. These data, from the regional cancer centres and the Princess Margaret Hospital, are in machine readable form from 1960 onwards. In addition to these records, the computerized cancer data base of the Foundation contains individual records on residents of Ontario who died from cancer since 1950; tabulations by sex, five-year age groups and site of cancer deaths from 1931 to 1983; individual records of patients diagnosed as having cancer in the province between 1964 and 1982; individual records of hospital discharges on patients with cancer from 1964 to 1983; pathology reports on specimens with cancer from 1972 to 1983. The total volume of records, in excess of three million, provides the Division with a unique opportunity for descriptive cancer epidemiology, and allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

Most of the staff of the Division is located in the Head Office of the Foundation at 7 Overlea Boulevard but the Research Unit of the Division is located in the Department of Preventive Medicine and Biostatistics at the Faculty of Medicine of the University of Toronto. Drs. Clarke, Kreiger, Marrett and Soskolne have cross-appointments in that department. This arrangement allows the staff of the Division to interact with other members of the epidemiological community as well as with medical and oncological colleagues.

In addition to the analyses of cancer incidence and mortality in the Province of Ontario, the staff of the Division are involved in a number of other projects. Some are collaborative, using registry data, with agencies such as the International Agency for Research in Cancer and the National Cancer Institute of the United States. Other studies are field studies conducted principally out of the Research

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**Epidemiologist, Division of Epidemiology and Statistics, OCTRF.

Unit; these include case-control studies of breast cancer, malignant melanoma, and acquired immune deficiency syndrome (AIDS) and its precursors. Most of the case control studies are supported by peer-reviewed grants.

CANCER INCIDENCE

In 1983, the Ontario Cancer Registry produced cancer incidence data for the entire province for the period 1964-1975. Late in 1984, incidence data up to and including 1982 were added, so that the registry now comprises information on more than 500,000 cases of cancer newly diagnosed in residents of Ontario between 1964 and 1982. The data presented in this report are provisional, because they do not include anyone who died of cancer but had not been registered while alive. When death data are added, the rates and frequencies will change somewhat.

The Ontario Cancer Registry employs a unique system of cancer registration, based on computerized record linkage of information on cancer cases collected routinely for other purposes and provided to the Foundation. The Registry receives more than 170,000 such records annually. The Ontario Ministry of Health requires that every hospital in the province provide diagnostic information on every patient discharged. This information is collected by an independent organization — the Hospital Medical Records Institute, and is provided to the Ministry in machine-readable form. Then, each year, the Ministry forwards to the Foundation records for the 100,000 hospital discharges with a mention of cancer. In addition, the Registrar General of Ontario supplies the Foundation annually with information on all deaths in the province (approximately 65,000 records) on magnetic tape. The Foundation also receives copies of 35,000 hospital pathology reports with a mention of cancer, submitted voluntarily by pathologists from about 95% of the province's hospital pathology laboratories. Information from these reports is abstracted and coded by Foundation staff and entered directly into the Foundation's own computer using an on-line system. Reports on patients referred to the cancer centres of the Foundation and the Princess Margaret Hospital, incorporating the Ontario Cancer Institute, are submitted either by magnetic tape or by an on-line system.

The same patient may be recorded in more than one of these files and more than once in the same file. To link together the large volume of data, Foundation staff have developed a sophisticated computer record linkage system based on the Generalized Record Linkage System (GIRLS) designed by Statistics Canada in conjunction with the National Cancer Institute of Canada's Epidemiology Unit. Since there is no one number, which uniquely identifies an individual throughout his/her life, linkage relies on a variety of identifying variables including name, date of birth, OHIP number (when available), hospital where diagnosed, and hospital chart number. A series of linkages is performed: first, hospital reports are linked internally to bring together multiple admissions for the same patient; second, pathology reports are linked to these aggregated hospital records, since most pathology reports will be generated during a hospital stay; third, this combined hospital-pathology file

is linked with previous years' incidence to identify new (as opposed to previously diagnosed) cases, producing the provisional incidence data shown in Tables I and II and Figures 1-3. Finally, deaths due to cancer and treatment centre records are linked to these provisional data. The usual effect of these last linkages is to add those cancers not identified during life — in the deaths due to cancer, and to improve the quality of data — in the cancer centre records.

In order to be able to report cancer cases rather than patients, the Registry uses a computer system known as "case resolution", again developed by Foundation staff. Case resolution examines all the linked records for a patient and determines the site of disease, the histology, the date of first diagnosis, and the method of diagnosis. Case resolution will also identify multiple primary neoplasms in the same individual.

The generation of incidence data for the province of Ontario by the Ontario Cancer Foundation is the result of a joint effort between the staff of the Division of Epidemiology and Statistics and the staff of Information Systems who together have developed these systems of record linkage and case resolution.

All incidence data presented are given in the Ninth Revision of the International Classification of Diseases (ICD9). While the Registry coded the primary site according to the Eighth Revision of the International Classification of Diseases between 1964 and 1978, all records have now been converted to ICD9; this conversion is fairly straightforward and will not have introduced any systematic misclassification, which would have affected time trends for any of the sites shown.

In the period 1980-1982, over 30,000 new cases of cancer were diagnosed annually in Ontario residents. Lung cancer is the most frequent malignant neoplasm in men (Table I). Cancer of the prostate is the second most commonly diagnosed cancer, but nearly 50% of these are found in men over the age of 75 years. Cancers of the main gastrointestinal sites are very important, together accounting for more cases than those of the respiratory sites combined. The bladder is also a common cancer site in men — 1189 new cases per year. There is evidence that several of the major male cancers are smoking-related, including lung, bladder, and lip and oral cavity.

In women (Table II), cancer of the breast is the most frequently diagnosed malignant neoplasm, accounting for 3875 (26%) of the cancers newly diagnosed in Ontario women each year. As in males, cancers of the major gastrointestinal sites are very common, particularly those in the colon and rectum. Respiratory neoplasms are much less common in females than in males. Together, the main gynecologic sites (cervix uteri, body of uterus, and ovary) account for 14% of the new cancers diagnosed annually.

Leukemia is relatively common in both sexes, ranking 6th and 8th in males and females respectively. Leukemia has a bimodal age distribution with peaks in early childhood and old age; solid tumors generally show a trend to increased frequency with increasing age.

Figures 1 through 3 show age-adjusted incidence rates over the time period covered by the registry. In Figure 1, it is evident that cancer incidence has increased

TABLE I

Average Annual Number of New Cases of Malignant Neoplasms in Males,
by Site of Disease and Age at Diagnosis, Ontario, 1980-1982
(Provisional data; see text)

SITE OF DISEASE	ICD9 ^a NUMBER	AGE AT DEATH (YEARS)																	All Ages	RANK ^b	
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown			
Lip and oral cavity	140-145	1	—	1	1	1	2	9	11	20	33	53	75	72	72	61	95	—	516	8	
Pharynx	146-148	1	1	—	—	—	—	2	2	8	10	14	25	23	23	15	12	9	138	—	
Esophagus	150	—	—	—	—	—	—	—	1	2	3	10	16	34	39	40	35	—	226	7	
Stomach	151	—	—	—	—	—	—	—	4	5	10	23	44	68	82	92	98	4	606	—	
Intestine, except rectum	152,153	—	—	1	1	1	5	11	15	33	54	100	161	201	273	257	443	3	1559	3	
Rectum and anus	154	—	—	—	—	—	1	4	8	18	36	70	111	121	157	144	217	3	894	5	
Pancreas	157	—	—	—	—	—	—	1	4	6	13	27	51	50	62	75	105	—	395	10	
Nasal cavities, middle ear and accessory sinuses	160	—	1	—	1	—	1	1	2	2	4	3	5	6	3	5	8	—	42	—	
Larynx	161	—	—	—	—	—	—	1	3	7	16	31	49	62	61	47	38	1	316	—	
Trachea, bronchus and lung	162	—	—	—	—	—	2	1	6	16	40	107	250	402	486	502	607	4	2991	1	
Bone	170	1	2	5	8	7	4	2	2	3	3	3	6	3	3	7	5	10	—	71	—
Connective tissue	171	2	1	4	5	5	5	5	5	7	8	8	11	12	10	8	16	1	113	—	
Malignant melanoma of skin	172	—	—	1	3	11	16	27	27	27	29	41	35	38	31	27	32	6	351	—	
Prostate	185	—	—	—	—	—	—	1	1	1	9	46	126	241	402	493	1045	8	2373	2	
Testis	186	3	—	1	6	23	36	34	17	13	11	5	7	3	3	4	2	—	168	—	
Bladder	188	—	—	—	—	2	7	11	17	23	43	78	113	139	196	223	337	3	1192	4	
Kidney and other urinary	189	4	2	1	1	2	1	3	7	11	22	44	60	66	67	53	73	1	418	9	
Brain and other nervous system	191,192	12	6	8	10	12	13	18	15	12	24	34	46	39	44	30	22	1	346	—	
Thyroid gland	193	—	—	1	4	3	6	8	8	6	7	4	7	6	7	3	6	—	76	—	
Lympho sarcoma and reticulosarcoma	200	1	2	2	6	5	5	5	10	10	15	22	30	36	37	35	51	2	274	—	
Hodgkin's disease	201	1	2	6	15	16	19	17	12	10	8	7	10	11	9	8	11	—	162	—	
Other lymphomas	202	4	3	3	5	6	4	6	12	14	21	21	29	32	35	27	45	2	269	—	
Multiple myeloma	203	—	—	—	—	1	1	1	2	4	6	15	21	30	32	30	61	—	204	—	
Leukemia	204-208	31	18	10	10	10	12	15	13	13	22	33	44	62	78	91	165	4	631	6	
Other and non-specific	Residual	22	5	1	11	6	14	15	24	35	55	102	152	190	234	210	359	8	1443	—	
TOTAL	140-208 ^c	83	43	45	88	116	156	208	240	336	589	1071	1678	2050	2543	2486	3982	60	15774	—	

ICD9 International Classification of Diseases, Ninth Revision, World Health Organization, 1977.
a. ICD9 International Classification of Diseases, Ninth Revision, World Health Organization, 1977.
b. Rank order for 10-14 year age group.

^aICD9 International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

^bRank order for 10 most common sites for site groups.

^cExcluding non-melanotic skin cancers ICD9 number 173.

TABLE II

Average Annual Number of New Cases of Malignant Neoplasms in Females
by Site of Disease and Age at Diagnosis, Ontario, 1980-1982
(Provisional data; see text)

SITE OF DISEASE	ICD9 NUMBER	AGE AT DIAGNOSIS (YEARS)																	All Ages	RANK
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+			
Lip and oral cavity	140-145	-	-	-	1	1	3	3	5	7	10	18	24	29	34	38	58	1	215	
Pharynx	146-148	-	-	-	-	-	2	2	3	1	1	10	6	7	7	7	11	3	55	
Esophagus	150	-	-	-	-	-	1	1	1	2	3	5	10	11	19	18	46	1	115	
Stomach	151	-	-	-	-	-	1	2	3	6	8	15	20	29	35	51	56	2	399	
Intestine, except rectum	152,153	-	-	-	-	-	1	1	1	1	2	5	10	11	19	18	46	1	115	
Rectum and anus	154	-	-	1	2	2	4	7	18	32	58	102	165	192	246	261	616	4	1710	
Pancreas	157	-	-	-	-	-	4	6	9	14	31	48	84	85	106	109	243	4	744	
Nasal cavities, middle ear and accessory sinuses	160	1	-	-	-	-	-	-	-	-	-	2	2	3	5	59	133	-	348	
Larynx	161	-	-	-	-	-	1	1	1	2	5	9	11	9	6	5	5	1	28	
Trachea, bronchus and lung	162	-	-	-	1	1	2	6	11	36	66	116	156	182	180	132	184	1	1074	
Bone	170	1	2	5	6	5	2	3	1	2	2	1	3	2	4	4	10	-	53	
Connective tissue	171	2	-	2	2	6	2	6	6	5	5	8	9	12	9	9	16	1	100	
Malignant melanoma of skin	172	-	-	1	5	18	36	40	32	20	40	33	36	30	26	25	40	6	398	
Breast	174	-	-	-	2	6	27	90	174	242	369	406	408	467	470	374	760	9	3064	
Cervix uteri	180	-	-	-	1	11	39	57	54	55	43	49	52	48	45	32	50	2	537	
Body of uterus	182	-	-	-	-	-	3	11	13	29	53	114	172	188	161	121	145	2	1013	
Other and unspecified uterus	179,181	-	-	-	1	1	2	4	3	4	4	4	5	4	5	6	14	-	57	
Ovary and fallopian tube	183	-	-	3	6	11	11	14	25	30	51	72	80	86	82	65	98	2	640	
Bladder	186	-	-	-	2	3	3	6	6	12	28	43	48	55	55	76	147	1	419	
Kidney and other urinary	189	4	4	1	1	1	1	2	8	6	10	19	28	27	33	34	46	1	226	
Brain and other nervous system	191,192	11	7	6	5	7	14	14	12	14	19	26	38	35	28	30	32	-	296	
Thyroid gland	193	-	-	1	10	17	21	22	13	13	15	15	18	13	11	11	21	-	211	
Lymphomas and reticulosarcoma	200	-	2	1	3	1	3	3	8	5	16	20	27	36	33	28	61	1	248	
Hodgkin's disease	201	-	1	6	12	16	16	12	8	7	7	4	4	7	8	8	12	-	123	
Other lymphomas	202	2	1	1	3	5	9	9	12	17	20	25	28	23	35	52	54	2	247	
Multiple myeloma	203	-	-	-	1	1	1	1	2	6	8	16	18	18	28	31	75	1	189	
Leukemia	204-208	20	16	9	8	6	9	11	20	12	20	25	31	33	50	62	142	6	480	
Other and non-specific	Residual	17	5	3	5	7	12	21	28	35	50	87	128	153	167	193	469	4	1364	
TOTAL	140-208	58	39	41	74	124	224	353	487	618	937	1291	1719	1824	1941	1796	3669	4	15280	

Dr. International Classification of Diseases, Ninth Revision

^aICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
Rank order for 10 most common sites (or site groups).

^bExcluding non-melanotic skin cancers (ICD9 number 173).

steadily since 1964 for both males and females, although cancer mortality over the same period has not changed. The rise in incidence rates may be due partly to continuing improvements in cancer registration, with respect to both completeness and accuracy, which has occurred until 1978. Since 1978, registration techniques and data sources have been of consistently high quality and completeness.

Figure 2 shows incidence trends for selected common cancer sites. Among males, the incidence is increasing for all of these. In more recent years, cancer of the trachea, bronchus, and lung does not show such a marked rise in men but is continuing to increase in women. Cancer of the prostate rose by 15% between 1973-75 and 1980-82, with no corresponding increase in mortality. As indicated earlier, almost 50% of newly diagnosed prostatic cancers are in men over the age of 75. It seems likely that the rise in incidence may be due partly to increased detection of this cancer in the elderly. The incidence of cancers of the intestine, except rectum, have also been rising steadily in men but not in women; the explanation for this is not clear. Cancer of the bladder shows a rising incidence, although mortality has been declining slightly; again, a diagnostic bias is suggested. Other cancer registries in North America show similar trends, particularly for cancers of the prostate and bladder.

Rates of lung cancer in women, unlike men, show a continuing rapid rise. Cervical cancer has declined markedly, while cancers of the ovary and breast have remained level. Cancer of the body of the uterus (endometrial cancer) has risen rapidly through the early 1970s and has since begun to decline.

Figure 3 shows trends in incidence and mortality rates for two less common cancers. The incidence of both testicular cancer and Hodgkin's disease remain essentially unchanged over the period of cancer registration in Ontario, while mortality rates began to decline sharply in about 1976 and 1967 respectively (the trends in male Hodgkin's disease rates are identical to those for females). These dates correspond to the introduction of new, more effective treatment for these neoplasms. More detailed studies of these trends are being conducted by the staff of the Division, using the registry data.

CANCER MORTALITY

Each year this section of *Cancer in Ontario* presents data on the most current year for which death certificates are completely enumerated and computerized. The Registrar General of Ontario has provided data on deaths due to all causes among Ontario residents for the year 1983. Figures 4-9 summarize these data, displaying, in bar chart and pie chart formats, the percentage distribution of deaths in major cause-of-death categories, by sex. Among both males and females, cancer accounted for 25% of deaths in 1983, surpassed only by diseases of the circulatory system.

The frequency and percentage of deaths in the same major cause-of-death categories are shown by broad age groups in Table III and Figure 7 for males, and in Table IV and Figure 8 for females. In the 0-14 year age group, cancers comprise only

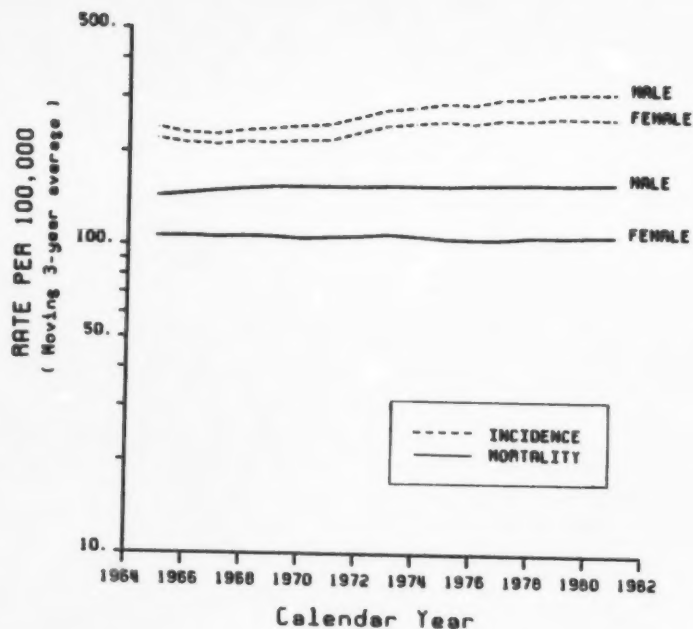
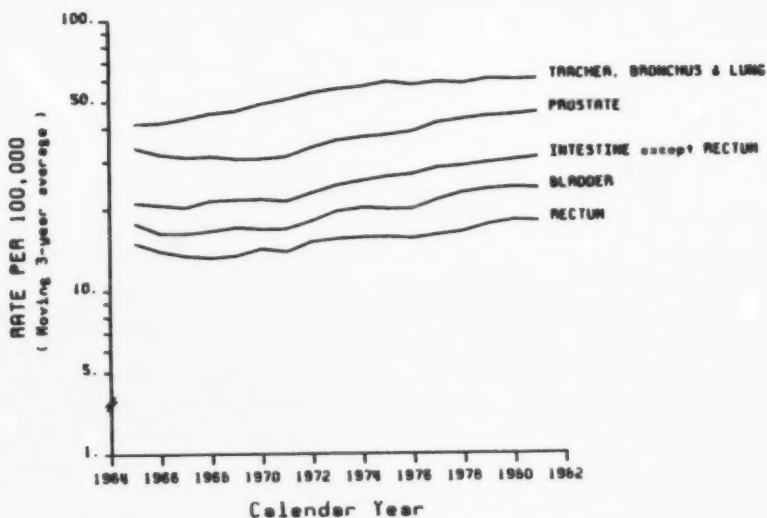


Fig. 1. Age-adjusted incidence (provisional and mortality rates for all cancer sites, by sex, Ontario, 1964-1982. (Age adjustment is to the world population.)

MALE



FEMALE

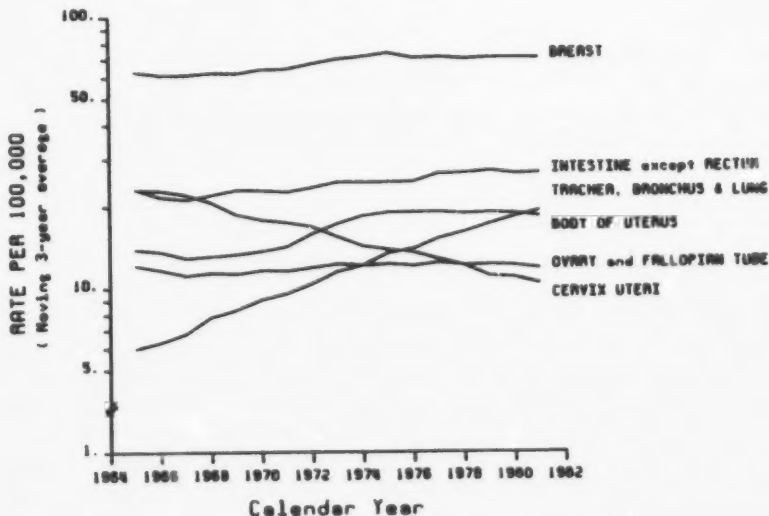


Fig. 2. Age-adjusted provisional incidence rates for selected cancer sites, by sex, Ontario, 1964-1982. (Age adjustment is to the world population.)

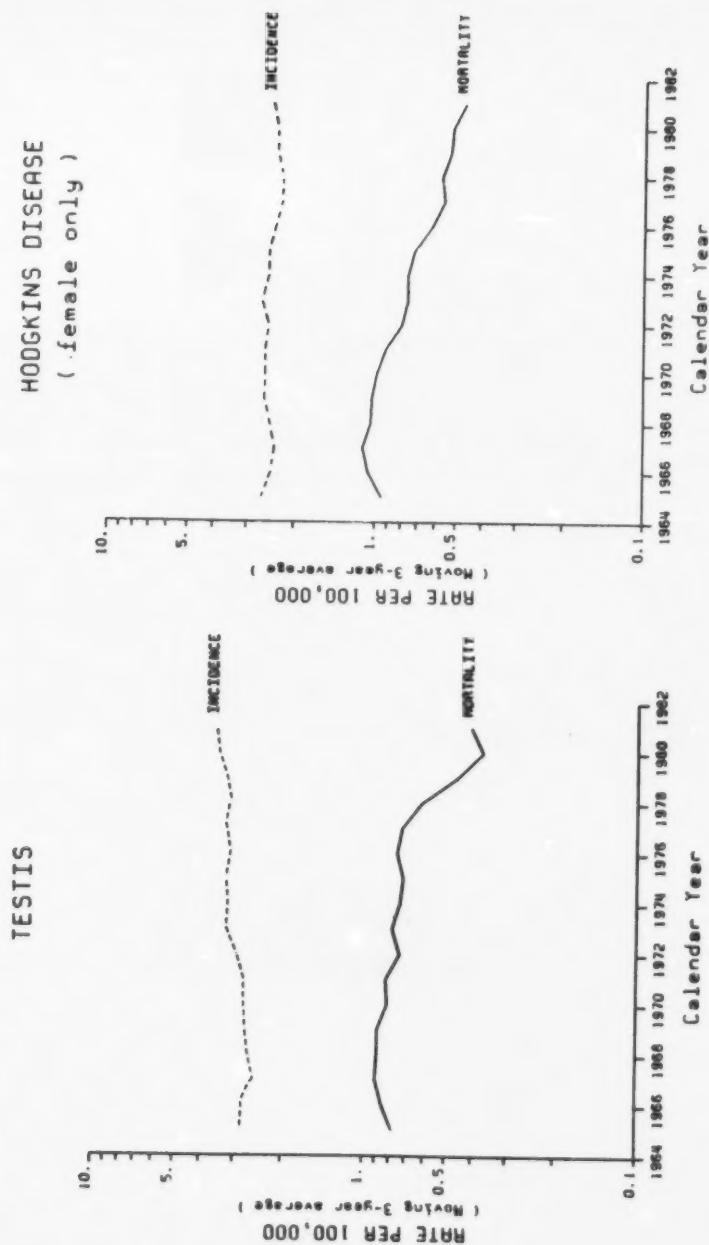


Fig. 3. Age-adjusted incidence (provisional) and mortality rate for testicular cancer and Hodgkin's disease, Ontario, 1964-1982. (Age adjustment is to the world population.)

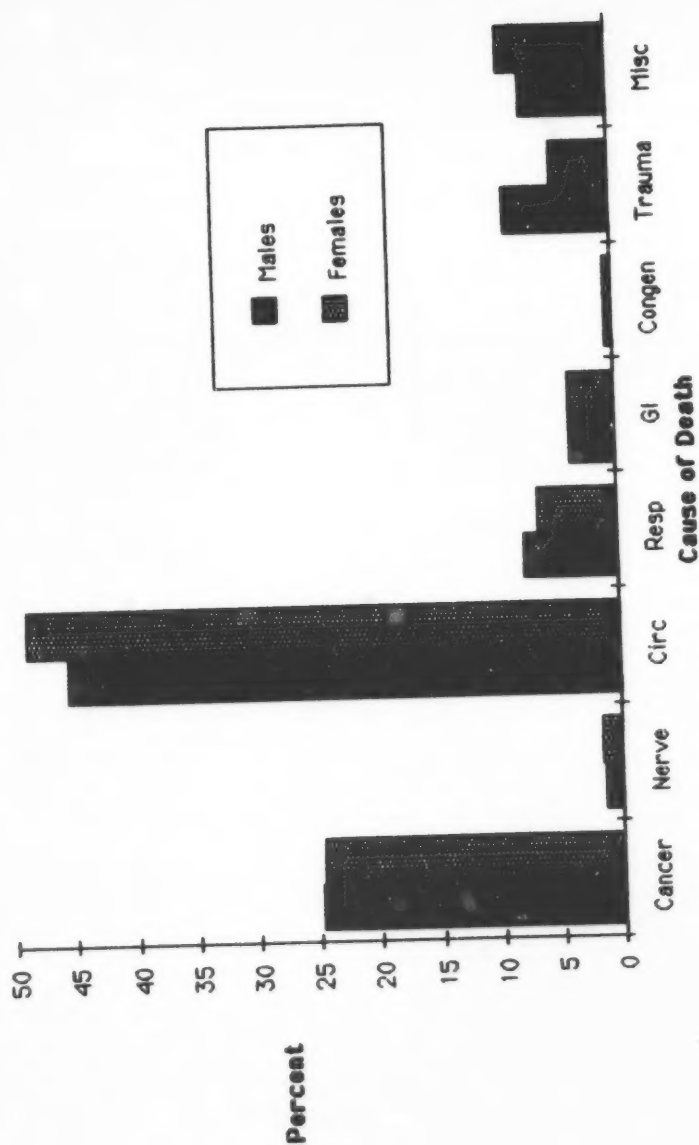


Fig. 4. Percentage distributions of major causes of death, by sex, Ontario, 1983.

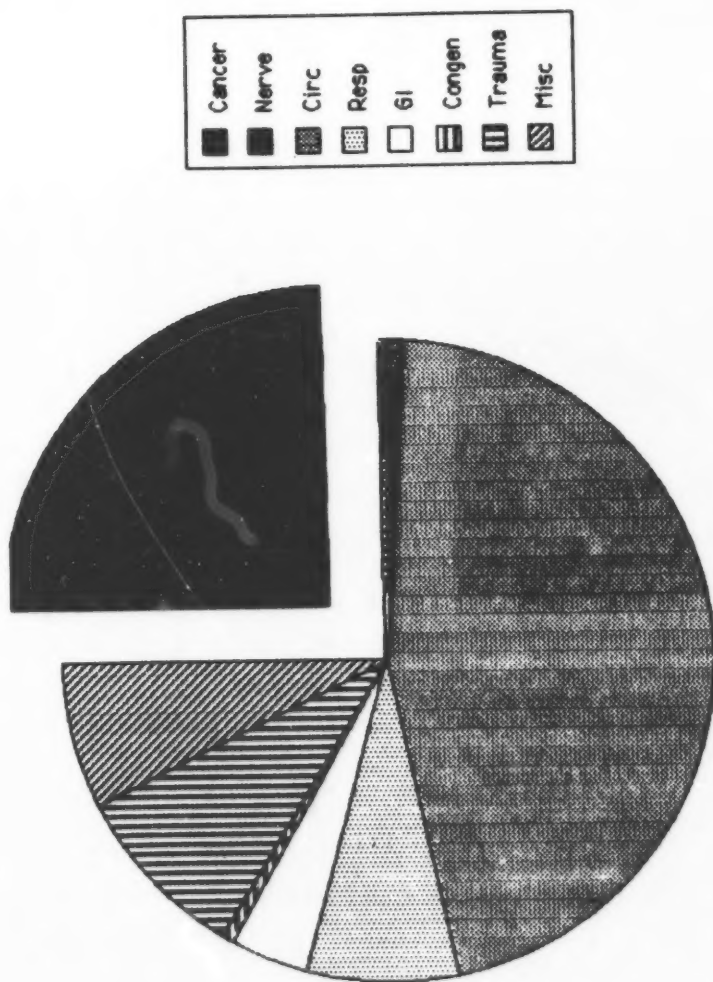


Fig. 5. Percentage distributions of major causes of death in males, Ontario, 1983.

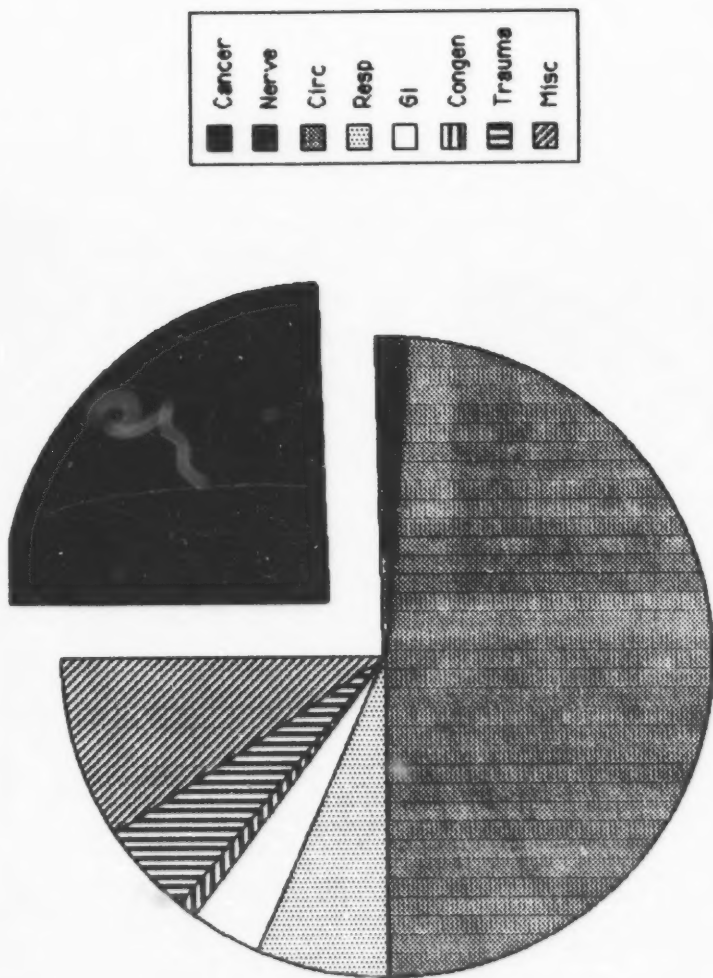


Fig. 6. Percentage distributions of major causes of death in females, Ontario, 1983.

TABLE III

Frequency (No.) and Per Cent (%) Distributions of Major Causes of Death in Males Within Age Groups, Ontario, 1983¹

CAUSE OF DEATH	ICD9 ² NUMBER	AGE AT DEATH (YEARS)									
		0-14		15-34		35-54		55-74		75+	
		No.	%	No.	%	No.	%	No.	%	No.	%
Malignant neoplasms	140-208	43	5	152	9	917	26	4,841	31	2,728	20
Diseases of the nervous system	320-389	37	4	36	2	52	2	189	1	210	2
Diseases of the circulatory system	390-459	11	1	88	5	1,337	37	7,353	48	7,093	53
Diseases of the respiratory system	460-519	29	3	28	2	100	3	969	6	1,612	12
Diseases of the digestive system	520-579	6	1	24	2	219	6	672	4	397	3
Congenital anomalies	740-759	184	22	26	2	13	0	19	0	5	0
Injury and poisoning	800-999	174	20	1,219	74	726	20	596	4	344	3
Other		374	44	72	4	226	6	841	6	997	7
ALL CAUSES	All	858	100	1,645	100	3,590	100	15,480	100	13,386	100

¹Omitted are five males of unrecorded age (including one who died of a malignant neoplasm) and one infant of unrecorded sex.

²ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

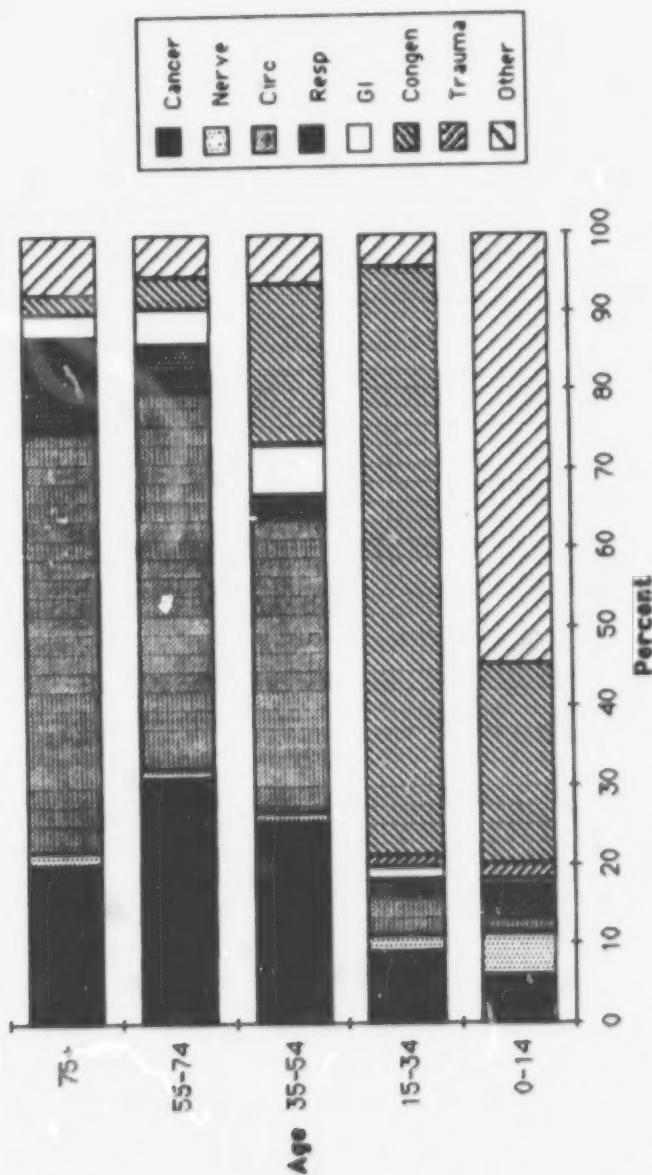


Fig. 7. Age-specific percentage distributions of major causes of death in males, Ontario, 1983.

TABLE IV
Frequency (No.) and Per Cent (%) Distributions of Major Causes
of Death in Females Within Age Groups, Ontario, 1983¹

CAUSE OF DEATH	ICD ⁹ NUMBER	AGE AT DEATH (YEARS)									
		0-14		15-34		35-54		55-74		75 +	
		No.	%	No.	%	No.	%	No.	%	No.	%
Malignant neoplasms	140-208	38	6	117	20	1,087	50	3,585	38	2,454	15
Diseases of the nervous system	320-389	21	3	22	4	44	2	180	2	232	1
Diseases of the circulatory system	390-459	19	3	38	7	428	20	3,683	39	10,213	61
Diseases of the respiratory system	460-519	18	3	26	4	54	3	523	6	1,301	8
Diseases of the digestive system	520-579	9	2	13	2	124	6	363	4	627	4
Congenital anomalies	740-759	175	27	14	2	7	0	15	0	8	0
Injury and poisoning	800-999	85	13	305	51	276	13	313	3	427	2
Other		277	43	61	10	134	6	736	8	1,439	9
ALL CAUSES	All	642	100	596	100	2,154	100	9,398	100	16,701	100

¹Omitted are three females of unrecorded age and one infant of unrecorded sex.

²ICD⁹: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

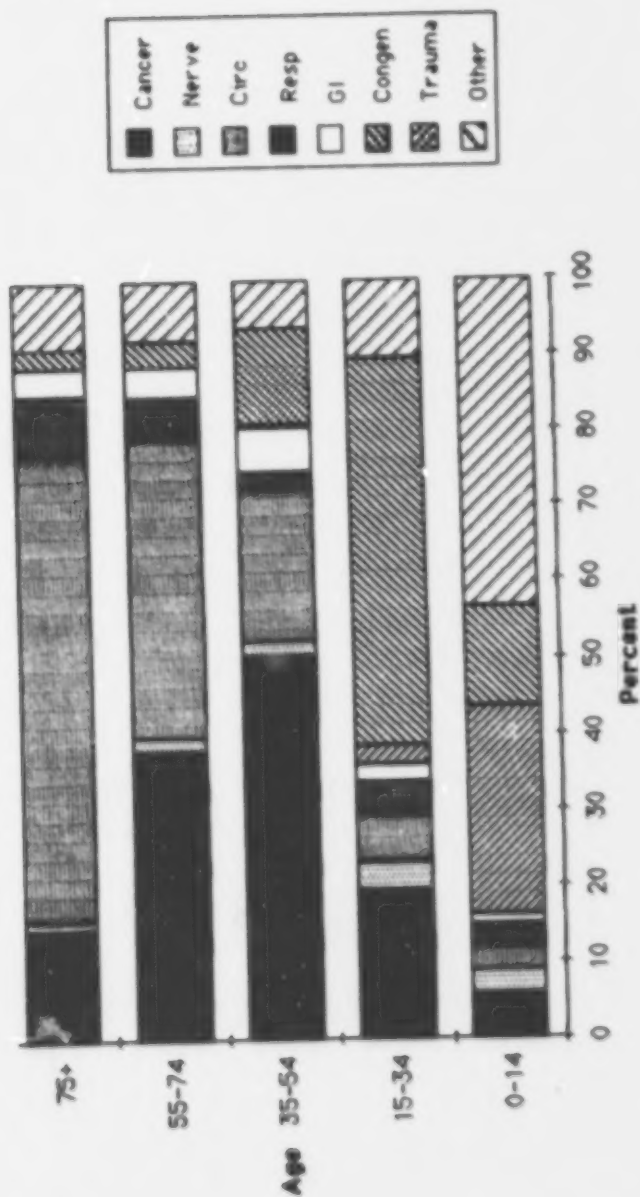


Fig. 8. Age-specific percentage distributions of major causes of death in females, Ontario, 1983.

5% of deaths; as would be predicted, congenital anomalies and injury and poisoning (trauma) rank as the two major causes of death. Fifteen to 34-year-old males die mainly of trauma. Among females in this age group, cancer starts to become the cause of a substantial proportion of deaths (20%) due to the relatively low frequency of traumatic deaths. In the remaining three age groups shown, deaths due to diseases of the circulatory system and deaths due to cancer predominate. An interesting difference between males and females is that for the former, cancer is the major cause of death in age group 55-74 years, while for the latter, it is the largest in the age group 35-54 years.

Cancer deaths are displayed in more detail in Tables V and VI, for males and females respectively. These tables are nearly identical in format and cancer site definitions (International Classification of Disease code) to those tables published in *Cancer in Ontario 1982*. The only differences are these: "ovary" now is combined with "fallopian tube", and "kidney and ureter" now is "kidney and other urinary". These changes have been made to render 1983 cancer mortality data comparable to the cancer incidence data presented in the preceding section. These latter data are available only in the format shown; for the time being, greater site specificity is not possible. It should be noted that the change in mortality site definition, from last year to this, has minimal effect. More than 98% of "ovary and fallopian tube" cancer deaths comprise "ovary", and 97% of "kidney and other urinary" deaths are "kidney and ureter".

In 1983, there were 8653 cancer deaths among males and 7273 among females. Lung cancer accounts for one-third of male cancer deaths, followed by prostate (9.4%), intestine (8.5%), and pancreas (5.2%). For females, while breast cancer is still the leading cause of cancer death, comprising 20.3% of such deaths in 1983, lung cancer is a close second (14.1%), followed by intestine (11.1%), ovary and fallopian tube (5.2%), and pancreas (5.2%).

The proportion of deaths submitted to autopsy varies greatly by cancer site. These data are shown in Table VII, with a graphical presentation in Figure 9. The range in percentage autopsies is from 5.6% for cancers of the nasal cavities, middle ear, and accessory sinuses, to 26.4% for Hodgkin's disease. In general, the leukemias and lymphomas are more often autopsied, as are the cancers which kill children (data on childhood cancers are presented in the following section of this report).

CANCER INCIDENCE AND MORTALITY IN CHILDREN

Table VIII shows crude average annual incidence and mortality rates per million population for children ages 0-14 years. For all sites of cancer, incidence was 163.2 and mortality 43.3 per million. The most common cancers in children are leukemia, brain, bone, kidney and Hodgkin's disease. The rank order of sites of fatal cancers in this age group are similar to the rank order of incident cancers, in that leukemia is the major cause of cancer death. Brain and other nervous system cancers rank second, followed by the other sites, which have mortality rates of 1-2 per million. It is clear

TABLE V
Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario, 1983

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age																			RANK ²	
SITE OF DISEASE	ICD ⁹ NUMBER	AGE AT DEATH (YEARS)													All Ages					
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64		65-69	70-74	75+		
Lip and oral cavity	140-145	-	-	-	-	-	-	-	2	1	2	8	19	23	12	21	38	134	14	
Pharynx	146-148	-	-	-	-	-	-	3	1	-	-	8	11	15	12	8	9	69		
Esophagus	150	-	-	-	-	-	-	-	1	2	7	14	21	46	48	48	64	251	9.5	
Stomach	151	-	-	-	-	-	2	1	7	5	11	19	44	58	65	67	153	432	5	
Intestine, except rectum	152,153	-	-	-	-	-	1	6	8	14	20	35	55	101	103	127	268	738	3	
Rectum and anus	154	-	-	-	-	-	1	1	2	1	9	13	26	38	50	56	103	299	7	
Pancreas	157	-	-	-	-	-	1	3	-	7	14	26	42	71	69	82	136	451	4	
Nasal cavities, middle ear and accessory sinuses	160	-	-	-	-	-	-	-	1	-	2	3	1	3	1	1	1	13		
Larynx	161	-	-	-	-	-	-	-	-	3	4	5	12	13	18	20	18	93		
Trachea, bronchus and lung	162	-	-	-	-	1	-	5	11	36	78	192	370	432	523	500	732	2680	1	
Bone	170	-	1	1	4	1	3	2	2	1	-	2	1	3	9	1	6	24		
Connective tissue	171	1	-	-	-	-	-	1	-	-	-	2	1	1	3	9	1	6		
Malignant melanoma of skin	172	-	-	-	-	2	4	6	6	6	9	11	16	16	8	9	12	105	15	
Breast	175	-	-	-	-	-	-	-	-	-	-	1	1	2	2	1	2	6		
Prostate	185	-	-	-	-	1	2	4	-	1	4	8	19	66	96	154	467	815	2	
Testis	186	1	-	-	2	1	2	1	1	1	2	1	1	1	1	1	1	19		
Bladder	188	-	-	-	-	-	-	1	2	-	1	7	16	24	32	49	138	270	8	
Kidney and other urinary	189	-	1	1	-	-	-	-	3	3	11	16	27	32	28	31	48	201	11	
Brain and other nervous system	191,192	2	2	1	4	3	6	7	11	8	14	17	31	47	34	23	41	251	9.5	
Thyroid gland	193	-	-	-	-	-	-	-	-	-	-	1	1	3	2	-	5	12		
Lymphosarcoma and reticulosarcoma	200	2	-	-	2	-	1	-	1	3	5	13	11	10	12	11	18	89		
Hodgkin's disease	201	-	-	-	-	3	6	1	4	4	4	6	19	17	20	26	56	194	12	
Other lymphomas	202	1	1	1	2	4	3	1	4	4	6	13	17	19	27	28	47	143	13	
Multiple myeloma	203	-	-	-	-	1	1	1	1	-	8	12	11	17	34	35	49	85	310	6
Leukemia	204-208	7	10	3	3	11	8	8	9	8	12	11	17	34	35	49	85	310	6	
Other and non-specific	Residual	5	2	-	1	5	6	6	5	10	23	36	78	98	140	116	252	783		
TOTAL	140-208	19	17	7	21	29	44	57	81	115	242	477	858	1181	1360	1435	2710	8653		

¹ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

²Rank order for sites with more than 100 deaths.

³Omitted are 31 deaths due to non-melanotic cancer of the skin (ICD9 number 173) and one death of unknown age.

TABLE VI

Number of Deaths due to Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario, 1983

SITE OF DISEASE	ICD9 ^a NUMBER	AGE AT DEATH (YEARS)														All Ages	RANK ^b		
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69			70-74	75+
Lip and oral cavity	140-145	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pharynx	146-148	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Esophagus	150	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach	151	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intestine, except rectum	152,153	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rectum and anus	154	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pancreas	157	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nasal cavities, middle ear and accessory sinuses	160	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Larynx	161	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trachea, bronchus and lung	162	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bone	170	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Connective tissue	171	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Malignant melanoma of skin	172	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Breast	174	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cervix uteri	180	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other uterus	179,181,182	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ovary and fallopian tube	183	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bladder	188	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kidney and other urinary	189	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Brain and other nervous system	191,192	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid gland	193	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphoblastoma and reticulosarcoma	200	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hodgkin's disease	201	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other lymphomas	202	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Multiple myeloma	203	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukemia	204-208	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other and non-specific	Residual	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL	140,208 ^c	12	14	12	12	17	29	59	127	200	262	479	720	839	1012	1014	2445	7273	

^aICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.^bRank order for sites with more than 100 deaths.^cOmitted are 17 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

TABLE VII

Number of Deaths Due to Malignant Neoplasms and Per Cent Autopsied, by Site of Disease, Ontario, 1983

SITE OF DISEASE	ICD9 ¹ NUMBER	NUMBER OF DEATHS	PER CENT AUTOPSIED
Lip and oral cavity	140-145	191	9.9
Pharynx	146-148	99	12.1
Esophagus	150	356	14.3
Stomach	151	700	9.7
Intestine, except rectum	152,153	1,545	8.0
Rectum and anus	154	495	7.1
Pancreas	157	830	13.6
Nasal cavities, middle ear and accessory sinuses	160	18	5.6
Larynx	161	111	10.8
Trachea, bronchus and lung	162	3,906	12.5
Bone	170	36	22.2
Connective tissue	171	54	16.7
Malignant melanoma of skin	172	190	10.5
Breast	174,175	1,481	8.4
Cervix uteri	180	227	12.8
Other uterus	179,181,182	216	8.8
Ovary and fallopian tube	183	381	10.5
Prostate	185	815	6.9
Testis	186	19	15.8
Bladder	188	389	10.3
Kidney and other urinary	189	322	13.6
Brain and other nervous system	191,192	428	15.9
Thyroid gland	193	40	20.0
Lymphosarcoma and reticulosarcoma	200	157	23.6
Hodgkin's disease	201	91	26.4
Other lymphomas	202	348	25.9
Multiple myeloma	203	265	10.9
Leukemia	204-208	609	21.3
Other and non-specific	Residual	1,608	11.9
TOTAL	140-208 ²	15,927	11.9

¹ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

²Omitted are 48 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

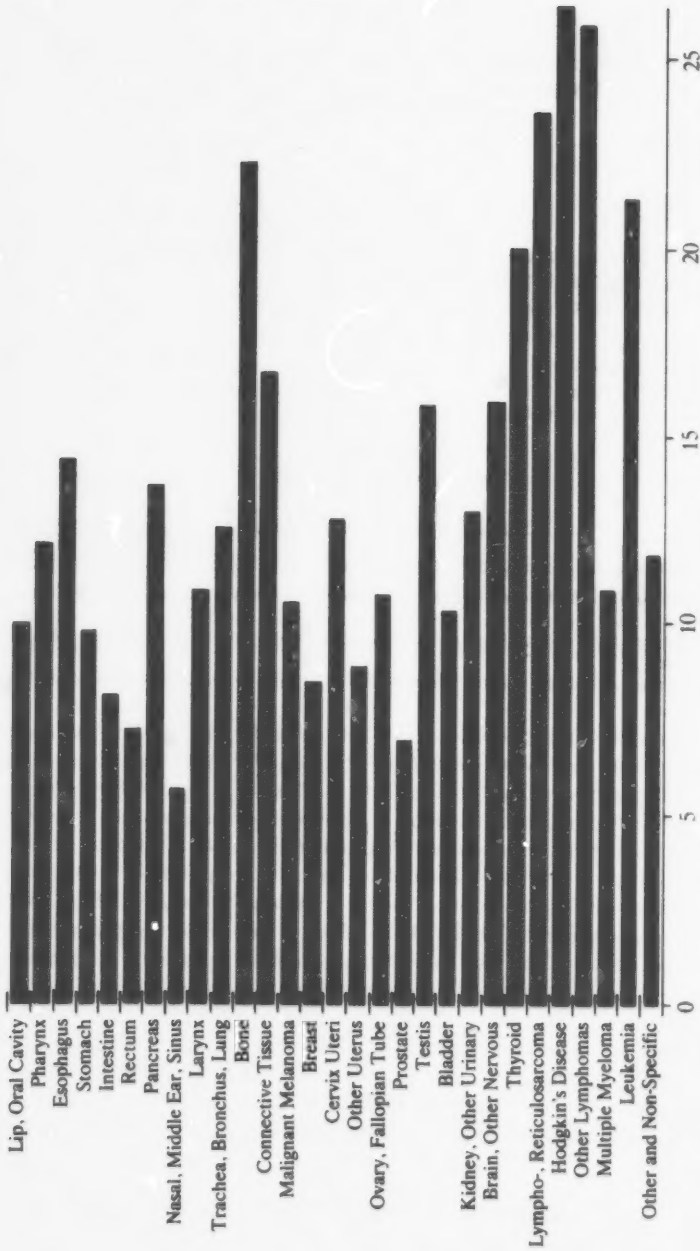


Fig. 9. Percentage autopsied by site of cancer death, Ontario, 1983.

TABLE VIII

Crude Rates of New Cases of, and Deaths due to, Malignant Neoplasms in Children, 0-14 Years Old, for the Major Sites, Ontario.

SITE OF DISEASE	ICD9 ¹ NUMBER	AVERAGE ANNUAL NEW CASE RATE PER MILLION 1980-1982	DEATH RATE PER MILLION 1983
Lip and oral cavity	140-145	1.6	— ²
Intestine, except rectum	152,153	1.1	—
Bone	170	8.4	1.6
Connective tissue	171	5.8	2.1
Malignant melanoma	172	1.1	—
Kidney and other urinary	189	8.4	1.6
Brain and other nervous system	191,192	26.4	9.6
Lymphosarcoma and reticulosarcoma	200	4.2	1.1
Hodgkin's disease	201	8.4	—
Other lymphomas	202	7.4	2.1
Leukemia	204-208	54.9	19.8
All Sites	140-208 ³	163.2	43.3

¹ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

²Indicates that fewer than two deaths occurred at that site in children in 1983, and therefore the rate is not calculated.

³Omitted are new cases of, and deaths from, non-melanotic cancer of the skin (ICD9 number 173).

that the leukemias and cancers of the central nervous system pose a major threat to health and life in the young.

POPULATIONS

Table IX shows sex- and age-specific population data for Ontario for the years 1981 and 1983, and for the "world". The 1981 Ontario population, which is based on the census, is provided for the purpose of calculating rates based on the 1980-82 average annual incidence frequencies. The 1983 Ontario population, which is a postcensal estimate, is provided for those who would like to calculate age-specific cancer mortality rates from the 1983 mortality data tabulated in a previous section. The world population is an artificial standard, one frequently used in calculation of age-adjusted rates. The Ontario population data are provided by Statistics Canada, and the world population is taken from *Cancer Incidence in Five Continents* by Waterhouse *et al.*

CANCER TREATMENT

Hospital Caseload

During the Ontario Ministry of Health's fiscal year 1982-83, there were 67,626 separations (discharges and deaths) from active and rehabilitation hospitals in Ontario in which the primary diagnosis was cancer. These accounted for 5.4% of all hospital separations and 1,040,136 days of hospital care. The average length of stay for cancer patients declined from 17.7 days in 1972 to 16.0 days in 1982-83*.

New Cancer Cases Registered at the Foundation Cancer Centres

In the last decade, the number of new cases registered at the cancer centres has increased by 45% from 13,272 cases to 19,305 (Table X). The greatest increase in the number of cancers registered was at the Toronto-Bayview Centre which opened in 1980. To assess these changes over time one must take into account the introduction in 1979 of the Ninth Revision of the International Classification of Diseases which separated the categories — in situ carcinoma and neoplasms of uncertain behaviour — from malignant neoplasms. In addition, in 1981, the Foundation returned to the international practice of counting patients with skin cancer as having only two lesions — basal-cell or squamous-cell cancer — and not as having multiple cancers of the same histology in different body sites. The distribution by cancer centre of the numbers of in situ lesions, neoplasms of uncertain behaviour and multiple skin cancers is shown at the foot of Table XI.

This increase in the number of cases seen at the cancer centres can be attributed in part to the great occurrence of cancer in the population during the last decade.

* Hospital Statistics 1982-83 published by the Ontario Ministry of Health.

TABLE IX
World Standard Population and Estimated Population
1981 and 1983, of Ontario
(In Thousands)

AGE GROUP	WORLD STANDARD ¹	ONTARIO, 1981 ²		ONTARIO, 1983 ²	
	MALE OR FEMALE	MALE	FEMALE	MALE	FEMALE
0-4	12.0	303.7	289.3	308.7	294.8
5-9	10.1	317.3	300.0	309.2	294.2
10-14	9.0	346.7	329.7	340.9	322.5
15-19	9.0	413.4	395.5	386.1	367.5
20-24	8.0	392.7	397.0	411.2	408.9
25-29	8.0	358.8	376.0	373.9	389.4
30-34	6.0	357.1	364.4	352.2	364.9
35-39	6.0	291.5	289.7	327.9	328.7
40-44	6.0	247.2	244.7	264.1	262.8
45-49	6.0	236.5	231.5	235.5	232.3
50-54	5.0	235.5	233.4	237.1	233.6
55-59	4.0	215.8	233.1	221.0	234.7
60-64	4.0	168.8	187.7	187.7	210.3
65-69	3.0	141.1	164.4	142.3	167.0
70-74	2.0	100.7	130.3	109.1	139.6
75+	2.0	120.0	211.7	128.6	228.7
TOTAL	100.1	4246.8	4378.4	4335.5	4479.9

¹Waterhouse, John et al (eds). Cancer Incidence in Five Continents, Vol IV. World Health Organization, Geneva, 1982, p.673.

²Source: Statistics Canada.

TABLE X*
New Cancer Cases Registered by Treatment Centre, 1974-1983^{1,2}

CENTRE	YEAR OF REGISTRATION										
	1974	1975	1976	1977	1978	1979	1980	1981	1982*	1983	
Hamilton	1,890	2,091	2,254	2,353	2,493	2,594	2,507	2,537	2,688	2,780	
Kingston	887	921	816	988	1,040	999	984	997	1,073	1,226	
London	2,254	2,359	2,460	2,344	2,488	2,537	2,583	2,529	2,563	2,748	
Ottawa	1,502	1,525	1,631	1,759	1,902	1,997	2,078	2,190	2,248	2,573	
Thunder Bay	313	313	399	365	412	369	401	462	444	435	
Toronto-Bayview	—	—	—	—	—	—	441	504	816	1,251	
Toronto, PMH	5,569	6,027	6,158	6,462	6,960	6,911	7,057	7,320	7,012	7,332	
Windsor	857	889	880	843	854	898	813	907	858	960	
TOTAL	13,272	14,125	14,598	15,114	16,149	16,305	16,864	17,446	17,702	19,305	

*Provisional (transition period — see text)

¹Excludes carcinoma of cervix in situ.

²Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

The increase is not unexpected because, in the last decade, the number of deaths has risen by 30% and there has been a similar increase in incidence although, as indicated earlier, some of the latter may be due to better registration. Probably these increases represent a combination of an increase in population in Ontario, which is also aging, and an increase in smoking-related cancers. These trends will continue each year, with an expected annual increase in the absolute number of new cases of cancer requiring treatment.

It should be noted that a "new case" registered at a Foundation cancer centre refers to a case of cancer seen for the first time during that year at any one of the Foundation centres. If a case is seen at two cancer centres in the same year, it is only considered in these tables as being seen by the first centre (1.7% of patients were seen at more than two centres in the same year). Also, it should be noted that a case may be new to the Foundation but may have been diagnosed some years before admission and be referred with metastatic disease; approximately 10% of newly registered cases fall into this category.

In Table XI, for 1983, the major sites of newly registered cancers were lung, bronchus and trachea (16.7%) and breast (15.7%) followed by skin, other than malignant melanoma (11.4%). Of the 17,652 cancers seen for the first time at one of the cancer centres, 14.5% were seen in Hamilton, 5.9% in Kingston, 13.3% in London, 13.5% in Ottawa, 2.3% in Thunder Bay, 6.6% at Toronto-Bayview, 5.0% in Windsor and 38.9% at the Princess Margaret Hospital in Toronto.

The location of the regional cancer centres and the associated peripheral clinics, and the type of outreach program, determine the referral pattern to each centre (Table XII). Thus, in Carleton County, where Ottawa is located, of the 1207 cases resident in the county, 1190 were referred to the Ottawa centre and only a small number to other centres. On the other hand, in Waterloo County, of the 368 cases resident in Waterloo County, 192 were referred to the London centre, 91 to the Hamilton centre, 80 to the Princess Margaret Hospital and five were referred to other centres. Four hundred and fifty-two residents of Quebec were referred to Foundation centres; the majority being seen at the Ottawa centres. An additional 160 residents of other provinces were seen at the Foundation centres, mainly at the Princess Margaret Hospital. Of the 173 residents of the United States and other countries, most were seen at the Princess Margaret Hospital, and the Ottawa and Kingston centres.

The data in Tables X through XII are marked "provisional" as implementation of the Patient Care Management System in the centres, from which this data is extracted, is not yet complete. However, we anticipate that the final data will differ only slightly from that presented here.

Seminars in Cancer Epidemiology

In the last academic year, the Foundation held two seminars. In November 1983, Dr. Calum Muir, Chief of the Descriptive Epidemiology Unit at the International Agency for Research on Cancer presented "The Role of the Cancer Registry in Cancer

TABLE XII*
New Cancer Cases Registered by Place of Residence and Treatment Centre, 1983

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Algonia	4		4	1	1	4	148		162
Brant	202		8	1		2	11		223
Bruce	5		80			1	42		129
Carleton	1	3	5	1190			8		1207
Cochrane	3	3	2	12	10	5	134		169
Dufferin	3					3	37		43
Dundas		3		30			33		33
Durham		1	168			30	321	1	353
Elgin			35		2	1	4		173
Essex	1	1					9	828	830
Frontenac		311		3			3		317
Glengarry			1	55			1		64
Grenville		39		23			1		63
Grey	6	2	80			6	111		185
Haldimand-Norfolk	113	1	68				2		184
Haliburton									
Halton	274	1	1	1		3	31		34
Hastings	2	233	1	5		12	153	1	443
Huron			121			3	58		302
Kenora	1	2			31		3		123
Kent	2		194						3
Lambton			268		1		2	28	226
Lanark		29		110			2	1	232
Leeds		157		11			2		141
Lennox and Addington	1	86		2			4		174
Manitowlin							5		94
Middlesex	1	1	720		1		17	1	18
Muskoka	1			2		2	9		33
Niagara	574		4			6	75		64
Nipissing	2	1	1	6		12	133		170
Northumberland						3			146
Oxford	1	14		2		10	98		123
Parry Sound	2		173			1	5		181
Peel	19		5	1			75		83
Perth	2		136			26	561		611
						1			164

TABLE XII* (Continued)
New Cancer Cases Registered by Place of Residence and Treatment Centre, 1983

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Peterborough	2	4	1			17	176		194
Prescott				68					68
Prince Edward		85	3	1		3	10		102
Rainy River				1	36				37
Renfrew		1		205		1	1		208
Russell									
Simcoe	2		2	48					48
Stormont				1			193		194
Sudbury	2	14		121		66	2		198
Thunder Bay	1			2	314		24		318
Timiskaming	11			1	1		78		98
Victoria	1	1		1	1	29	96		128
Waterloo	97	1	192	2		3	80		380
Wellington	163		2	7		4	241		418
Wentworth	1025			1	1	2	15		1046
York	4	4	8	1		866	339	4	1195
Quebec									
Other Provinces	15	4	17	412		4	25	1	457
U.S.A.	3	22	11	25	3	0	80	6	184
Other World	4	2	3	16	1	1	15	8	84
Residence at diagnosis not stated	9	2	3	11	1	19	43		89
TOTAL	2559	1045	2340	2588	403	1173	6875	884	17676

*Provisional transition period - see text.

In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.

In 1974 the counties of Durham and Lindsay became the Regional Municipality of Durham. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expanded by parts of Durham and Ontario.

In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand Norfolk.

Control". In January 1984, Dr. Jan Muller and Mr. Robert Kusiak from the Ministry of Labour presented the results of the recent Ontario Miners' study. Attendance has declined in recent years with the initiation of more seminars at the universities in Ontario. For the future, we propose to conduct a single one-day seminar featuring three topics, hoping that this forum will provide the opportunity for interaction between cancer epidemiologists in Ontario.

ACKNOWLEDGEMENTS

We acknowledge with gratitude the continuing co-operation of government. The Ontario Ministry of Health has provided source records and advice; the Office of the Registrar General of the Ministry of Consumer and Commercial Relations has provided computerized data on deaths due to all causes in Ontario residents and, in addition, has provided facilities for an on-site search of their records for treatment evaluation and other research. We appreciate the assistance of the staff of the Hospital Medical Records Institute (HMRI) and are indebted to the medical records staff of all hospitals in Ontario who willingly and promptly provided additional information, primarily for the generation of incidence data, but also to ensure the high quality of data entered into the cancer registry.

We extend a special thanks to the Directors of the regional cancer centres and the Princess Margaret Hospital and their Managers of Health Records for support during the year, and to the members of the Foundation's Standing Committee on Records and Statistics and its sub-committees.

The assistance of all the staff of Information Systems in the processing of the Foundation's large data base, is acknowledged with gratitude. In particular, we thank the individuals working under the direction of Mrs. June Murphy and Mr. Tom Broz, who have generated incidence data up to and including 1982.

Our special thanks are extended to Mrs. Mary Nemes, Manager of Health Records in the Division, Miss Darlene Dale, Supervisor of Cancer Registry Records, and the staff of the Division for their dedication to the generation of incidence data and their continual effort to improve the quality of the cancer registry. We are also grateful to Mmes. Margaret Holman and Sheila Wing for their help in preparing this report and to the staff of the Research Unit, at the University of Toronto, for their statistical and clerical skills which make possible this report.

INFORMATION SYSTEMS



OVERVIEW OF INFORMATION SYSTEMS

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In 1980, the Ontario Cancer Treatment and Research Foundation embarked upon an ambitious program to upgrade its computer facilities. At that time, small mini-computers, Digital Equipment Corp. (DEC) PDP 11/34s or equivalents, were installed in each of its regional cancer centres for use in radiotherapy planning. One such minicomputer was also installed at the Foundation's Head Office for the Ontario Cancer Registry, which is operated under legislative mandate through the Division of Epidemiology and Statistics. Stored on this computer was a brief record of all new cancer cases referred to Foundation centres from 1964 onward, and hospital discharge summary records for oncology patients for the same period. The Office of the Registrar General had been providing death information on individuals whenever cancer was the cause of death or underlying cause of death. This information was also stored on the Registry computer.

In 1972 some of the province's pathology laboratories had begun to supply paper copies of their reports on specimens diagnosed as malignant. These reports were coded, key punched by an external service bureau and added to the computer system.

Ontario has no unique health identifier, nor does it have mandatory reporting of cancer patients to the Ontario Cancer Registry. Thus the Foundation was faced with the task of linking together all the records from the various sources to identify, first individual patients, then their diseases. For any given year these cases are referred to as "cancer incidence". It is important to avoid overcounting especially when a patient may have records from several sources and even multiple records from the same source.

For data for the years 1969-71, the Registry used primarily manual techniques with some assistance in sorting and grouping of records by a General Electric Mark I computer, which had been donated to the Foundation by Canadian General Electric Co., Ltd. Incidence for 1969-71 was not generated until 1977 because of the difficulty of manual identification on the volume of records linked. As the organizations supplying the data shifted to computerized systems and the number of laboratories supplying data for the Foundation increased, it became evident that manual techniques were totally inadequate. The Registry only could create the necessary "linkages" if it

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acquired adequate computer facilities. The DEC PDP 11/34 computer, which had replaced the Mark I, did not have the capacity to handle and manipulate such massive quantities of data. At the same time it was recognized that the regional cancer centres required improved computer facilities not only for the planning of radiotherapy but also to support patient-care management and administrative applications.

In August 1978, the Foundation's Computer Advisory Committee recommended the engagement of an independent consultant to review existing computer facilities and to describe a system that would assist future developments. Various firms submitted proposals and the Committee selected Systemhouse Inc., a Canadian consulting firm specializing in data processing. Systemhouse began their assignment in March 1979. Their study consisted of six major phases:

- Review of the data-processing requirements within the Division of Epidemiology and Statistics, including the Ontario Cancer Registry.
- Visits to all Foundation centres to assess their data-processing requirements.
- Review of data-processing relationships within the Ontario Cancer Institute.
- Review of the Foundation Data Centre.
- Detailed review of the Hamilton Centre to determine the requirements for a regional patient-care management system.
- Formulation of the entire Foundation's data-processing requirements and recommendations for future developments.

On October 16, 1979, Systemhouse issued its report entitled "The Ontario Cancer Treatment and Research Foundation: Assessment of Current and Future Data Processing Requirements". This report recommended that all computer applications developments and hardware software acquisitions be "frozen" until a manager of Information Systems could be hired. Then this manager would develop a plan to implement the report's recommendations directed to meeting the Foundation's computing needs. In June 1980, a manager was hired and, following the same methods as Systemhouse, confirmed and updated the report.

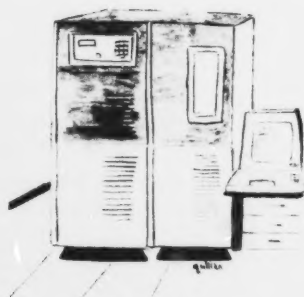
In the summer of 1980, Information Systems' staff held preliminary discussions with vendors who offered systems which might satisfy the Foundation's requirements. Other clinics, hospitals and cancer registries were visited to examine operational systems that might be appropriate. Then a request for proposal (RFP) document was prepared and submitted to vendors on October 29, 1980. This RFP spelled out the computing requirements of the Division of Epidemiology and Statistics for the Ontario Cancer Registry and for its service and research projects. It also described the conceptual requirements for the first phase of the Patient Cancer Management System (PCMS). Also it identified the anticipated financial and administrative applications.

The Foundation then established a Committee on Information Systems to advise on policies related to Information Systems. It also formed the Technical Subcommittee to advise on technical issues and a Computer Users Group to identify user requirements. The Committee on Information Systems assisted by the Technical

Subcommittee reviewed the merits of each of the systems proposed in response to the RFP and recommended acceptance of the proposal submitted by CyCare, Canada Inc. Subsequently this recommendation was confirmed by the Executive and Financial Committees and the Board of the Foundation.

In March 1981, the Foundation prepared a submission to the Ministry of Health to support the proposed computerized system recommended by the Committee on Information Systems. As a result, the Ministry engaged an independent consulting firm to evaluate the Foundation's requirements and the technical solutions proposed. The consultant presented his report to the Ministry in mid-July 1981 and recommended that the Ministry support the Foundation's request. His report confirmed the Foundation's statement of requirements and proposed solutions.

In November 1981, the Foundation installed a Honeywell DPS 6/92 computer at its Head Office. On January 1, 1982, new standardized manual systems were implemented in the regional cancer centres, while Information Systems working with CyCare was finalizing the design of the centres' PCMS. In this period, Information Systems staff proceeded with the design of the new Ontario Cancer Registry System.



In March 1980, Statistics Canada agreed to provide computer processing services and software, which would allow the Foundation to begin linking its records to identify individual cases of cancer and so eliminate duplicates. By the end of 1984, this project, known as the incidence "catch-up" project was intended to bring provincial incidence data up to 1982. The processing of records from various sources such as pathology reports, hospital discharges, death certificates and regional cancer centre registrations was handled by a generalized interactive record linkage system (GIRLS) developed by Statistics Canada. In January 1982, this linkage process was transferred to Toronto, using the facilities of a data centre operated by the Ministry of Government Services.

In approving the overall computer plan for the Foundation, the Committee on Information Systems had recommended that radiotherapy planning in all centres be

handled on specialized "stand-alone" equipment that would be standardized across all Foundation centres. Also this committee recommended that large-scale scientific processing continue to be handled on local university computers.

COMPUTER HARDWARE

Through the generous support of the Ministry of Health and the Canadian Cancer Society Ontario Division, the Foundation now has sophisticated computer facilities in its regional cancer centres and at its Toronto Head Office. Each centre (except the Toronto-Bayview, which shares the Head Office computer), has its own Honeywell DPS 6 minicomputer with terminals throughout the centre. Data entered on these computers are transferred weekly to the Head Office system for use by the Registry. The centres and Head Office also have local networks of IBM personal micro-computers for managing financial data and for word processing. The Head Office network interacts with the local networks to transfer financial data. Also computers have been installed at two outreach clinics. The Rotary Club of Preston-Hespeler paid for the hardware and communication services to link the oncology unit of the Cambridge Memorial Hospital to the Hamilton Regional Cancer Centre's Honeywell computer. The oncology unit at St. Joseph's Hospital in London has a computer linked to the London Regional Cancer Centre. Additional outreach links are planned for 1985/86.

In September 1984, the Foundation Board approved the recommendation that the Foundation continue to use the GIRLS program as the basis for its record linkage process and that an in-house IBM 4361 computer be acquired to run this system. Operation of its own computer would allow the Foundation to reduce the cost of Registry computer processing, and also to respond more economically to requests to link external research files to the Registry data base. Figure 1 shows the typical configuration of a regional cancer centre; Figure 2 shows the entire Foundation hardware network.

COMPUTER APPLICATIONS

The cover of this issue of *Cancer in Ontario* depicts the interlocking character of all of the current computer applications or planned as future projects. These projects are developed and managed in several functional areas, as follows.

Ontario Cancer Registry System

Information Systems' highest priority has been to provide the programming and computing resources for the incidence "catch-up" project. By the fall of 1983 preliminary incidence data were available for the period 1964-1975 and the Division of Epidemiology and Statistics undertook to analyze these data and ensure their accuracy. The application of internationally accepted indices of reliability demonstrated

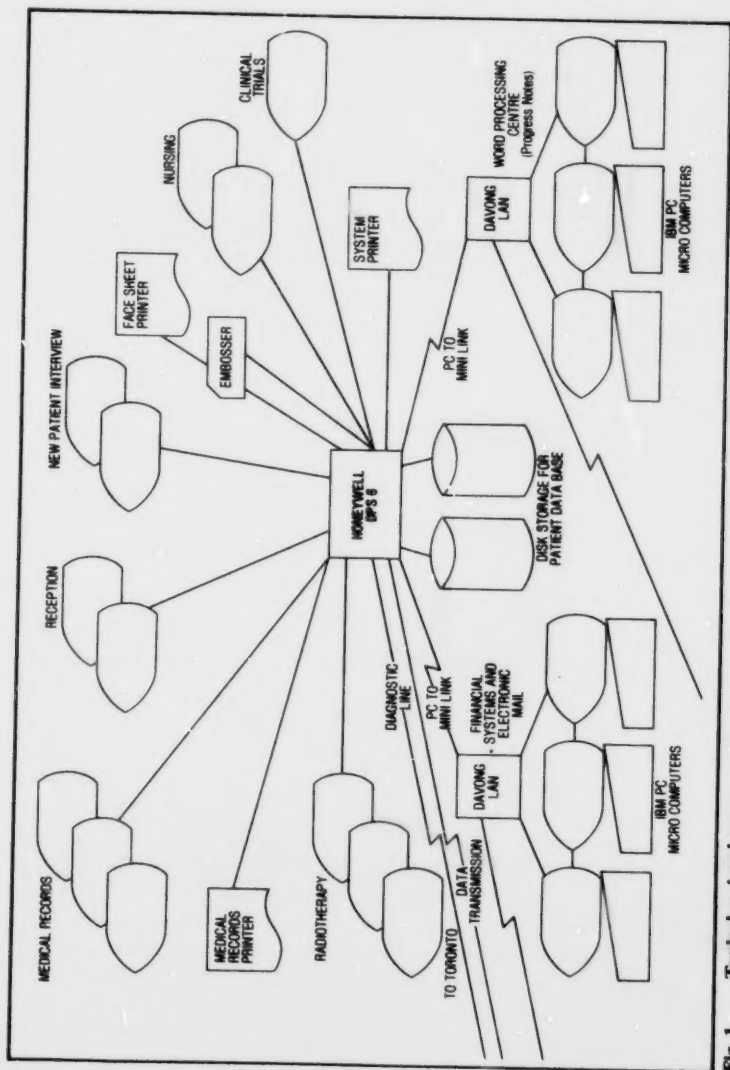


Fig. 1. Typical regional cancer centre computer hardware configuration. Each centre has a DPS 6 minicomputer with video display terminals located in all areas. Centres also have two LANs - one for progress notes and the other for financial, word processing, and research applications. The Honeywell systems have diagnostic and data transmission lines to Head Office. Communication lines connect the LANs and the DPS 6s between the centres and Head Office.

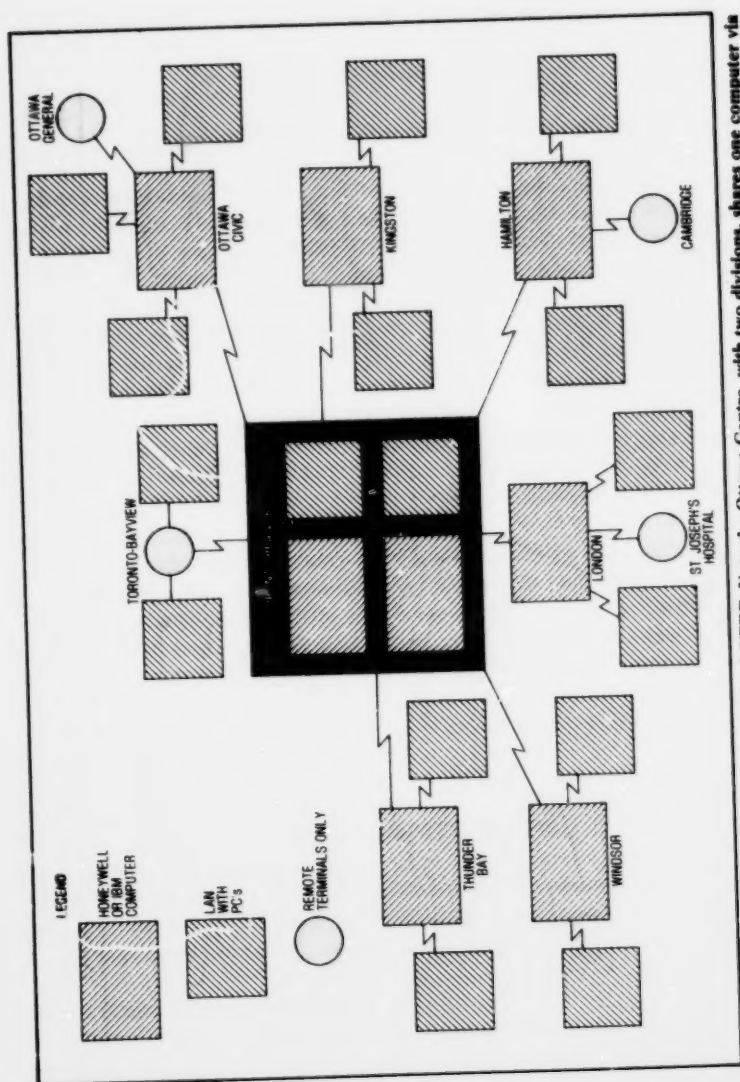


Fig. 2. Computer hardware network of the OCTRF. Note the Ottawa Centre, with two divisions, shares one computer via communication lines similar to those connecting the Toronto-Bayview Centre with Head Office. Also shown are two outreach clinics.

that the computer techniques used by the Foundation produced satisfactory results, which were comparable with those produced by other population-based registries. Preliminary incidence data are now available up to 1982, but this will become final only with the addition of cases identified only by death certificates. By the time *Cancer in Ontario 1984* is published, the incidence data will be complete. Then the Division of Epidemiology and Statistics will begin the analysis of the data, in anticipation of its publication for an international audience.

The Ontario Cancer Registry System consists of five major components.

Record Linkage. Using GIRLS software, linkages are performed on one or two files at a time. All records with similar sounding surnames are compared to each other, using all available patient-identification information. The data items vary by source but usually include names, birth date, sex, residence, and OHIP number. A typical linkage which draws on hundreds of thousands of records may involve tens of millions of comparisons. The decision as to whether two records refer to the same individual uses probability theory. Items so compared do not have to be identical to constitute an agreement. The system assigns "weights" (numerical scores) to each comparison outcome. The magnitude of the weights is determined by the level of agreement (or disagreement) between the two variables. The sum of all weights for a specific pair of records must exceed a predetermined threshold before that pair of records is linked. Links with weights just above or just below the threshold are re-examined by qualified medical records staff within the Division of Epidemiology and Statistics and occasionally human decisions may override those of the computer programs.

Death Clearance. It is the process of identifying deceased patients in the Registry, and then determining their date and cause of death. Using GIRLS, the Registry file is linked to a file of all deaths occurring in Ontario. For the period 1964-1982 the computer will link approximately 500,000 registry records and one million death records. Incorporation into the registry of information from the matching death records will make it possible to use the Registry file for survival analysis, and will enable the Registry to provide "passive" follow-up on patients.

Case Resolution. After source records for each patient are brought together by record linkage they are processed by the Case Resolution System, which was developed through joint efforts of Information Systems and the Division of Epidemiology and Statistics. It determines the site of the primary tumor, the histology, the date of diagnosis, the method of confirmation and the patient's residence at diagnosis. Multiple primaries in the same individual are also identified and reported.

A complex algorithm is employed to get the most specific disease information, taking into account the relative reliability of different data sources. Reports are produced showing any unusual or unexpected situations. Finally the system produces one record for each primary case of cancer. These records then form the basis for incidence reporting.

Incidence. Case records created in case resolutions are counted and summarized to provide case-frequency counts for each year of diagnosis, site of cancer, county of

residence sex and age. These numbers then are divided by the corresponding population figures provided from the census by Statistics Canada to give cancer incidence rates. These can be adjusted further for the age distribution of the population to make them more comparable with rates from other jurisdictions. Several indices are calculated to evaluate the quality and accuracy of the rates. These include proportion of cases reported by death certificate only, the proportion of cases confirmed histologically, and the ratio of mortality to incidence rates.

Mortality. Rates are calculated in a similar way by the same computer system as incidence rates. The cause of death is stated clearly on each death record. Mortality rates have been calculated for the period 1931-1983 and have been made comparable over time by creating a detail dictionary prepared by the Division of Epidemiology and Statistics based on original work in the period 1930-1970 by Dr. A. H. Sellers. The dictionary equates site of disease definitions based on six different revisions of the International Classification of Diseases (ICD).

Registry Data Collection System

At present, the Registry uses five external data sources to generate incidence data. Some sources are received in machine-readable format, while others come as paper documents. The data collected at the regional cancer centres by the PCMS is transmitted to Toronto and also becomes a source of registry data. Currently an interface is being developed to allow transmission of Ontario Cancer Institute patient data automatically to the Registry. The individual collection systems for the five external sources are described below.

Pathology. Most pathologists in Ontario voluntarily submit photocopies of all reports with a malignant diagnosis and, in 1984, more than 40,000 were received. Data from these reports are abstracted and coded by trained medical records staff in the Division of Epidemiology and Statistics. Then they are entered into an online data entry system, which was designed and developed by Information Systems. As data are entered they are edited immediately for validity, consistency and reasonableness. Validity "edits" reject data which are invalid in themselves, e.g. the 13th month or 32nd day. Consistency edits compare two or more data fields and report contradictions, e.g. male patient with ovarian cancer, or treatment date before the date of birth. Edits for reasonableness report suspicious but possible real conditions, e.g. a patient is 120 years old or five-year-old male has prostatic cancer. The system also requires that certain data elements such as patient's surname, date of test, and site of disease always be entered. After an entered report passes all the edits successfully, it is stored in the Registry source data base. The system allows the user to display, to update or even to delete previously stored records. When updating an existing record, edits are again performed on all information affected by the change.

Steroid Receptors. Tests for steroid receptors usually are performed on tissue biopsied from breast cancer patients. Occasionally other cancer sites are also tested. This test program is funded by the Ministry of Health and administered by the Foundation. The participating laboratories submit to the Foundation on worksheets

or computer printouts identification information on patients and their disease. Recently an online data-entry system has been completed for the steroid receptor data. The data entered through this system will become part of the Registry data base and will be available for special studies.

Carcinoembryonic Antigens (CEA). Tests for CEA are performed on specimens from cancer patients, and the Ministry of Health pays for these tests through the Foundation. Test results are submitted to the Foundation with patient and disease information. Data from Sunnybrook Hospital are transmitted via communication lines thus eliminating the need for data entry at the Foundation. At present other laboratories submit their data on paper. Information Systems is developing an online data entry system similar to the ones used to enter pathology and steroid receptor data. With the introduction of microcomputers in many laboratories, we expect that data will be more frequently received in machine-readable form.

Death. The Office of the Registrar General's death file is a major source of Registry data. It not only helps find cases identified by a death certificate, but it also provides dates and causes of death for Registry patients. A consolidated file for the years 1950-1983 is nearly completed. In the 1950-1963 period, only cancer deaths records are available. Starting with 1964 the file will contain deaths from any cause. This file of more than two million records will be available for online display with access by the patient's name and by the death certificate number.

Hospital. All hospitals in the province supply information about each hospital separation to the Hospital Medical Records Institute (HMRI). The HMRI provides a magnetic-tape copy of these data to the Ministry of Health. The Ministry also creates a computer file from the 106D forms filled out by all hospitals business offices when patients are discharged. The HMRI file has excellent diagnostic information and records up to 16 diagnoses and 12 procedures; however, this file lacks patients' names. In order to provide these names, the Ministry links the HMRI records to the 106D records using hospital number, admission date and register number.

From the resultant file, the Ministry selects all records with at least one cancer diagnosis and provides this file to the Foundation where it becomes a part of the Registry data base. In 1986, an online facility will be added to the data collection system, which will display and update hospital records in a manner similar to that described for other sources.

Administrative Systems

The Foundation has begun to automate several administrative processes. These are described briefly below.

Word Processing. Each of the regional cancer centres received a local area network of IBM personal computers in 1984. Word processing is, by far, the most used software on these microcomputers because it simplifies the revision of manuscripts, research papers, manuals and other documents.

Financial Systems. A general ledger package was the first computerized financial system implemented in the centres. Accompanying this was "SYMPHONY" — a



spreadsheet package used to prepare budgets and analyse financial information. Other planned financial systems include accounts payable and fixed assets.

OHIP Billing. This system will be implemented on the Honeywell minicomputers. Submissions to OHIP will be consolidated at Head Office and forwarded via magnetic tape. Reconciliations return in a similar manner and will be printed at each centre.

Electronic Mail. An electronic mailing system provides fast and reliable transmission of letters, memoranda, minutes, agenda and other documents. The information as sent may have been entered through the word processing system or through the electronic mail package. Its destination may be internal or external to the centre. A Foundation-wide electronic mail facility will be established in 1985.

Workload. A series of programs will be available in each centre to provide up-to-date statistics on the data on radiotherapy, chemotherapy, procedures and visits, which have been entered through the medical services reporting system. The workload figures will detail current period totals and year-to-date information. The data can be requested for a particular period and printed by resource, site of disease, or by time period. Both raw counts and summarized results can be printed optionally.

Information Centre "Hotline". An information centre with a "hotline" service has been set up to handle the calls and questions from users of any Foundation computer system. The "hotline" staff will be able to provide information to appropriate people and assist in the resolution of questions and/or problems from Foundation computer users. The information centre also handles many of the requests for statistics and data which are sent to this department for processing. In 1984, over 200 such requests were handled.

Project Management. Software on the IBM microcomputers is being used to plan, schedule and monitor the life-cycle of Information Systems' projects. Weekly and monthly reports are available by project or person.

Patient Care Management System

The Patient Care Management System (PCMS) is provided by CyCare Systems Canada Ltd. The implementation of this system began in the Ottawa Regional Cancer

Centre during the spring of 1983 and by fall of the same year each regional centre had a minicomputer installed.

PCMS provides up-to-date patient information through video display terminals in an online mode throughout the centres. It contains extensive data-editing facilities to ensure the accuracy of records being stored on the data base. It also includes appropriate security, error recovery and audit modules to maintain the integrity of the files.

PCMS is made up of many integrated modules, which work together, to assist in the management of patient care. All data are available in display mode on all terminals to all authorized users. However, adding, updating and deleting of data is restricted to those users who are responsible for the information in the individual components of the system. The following paragraphs describe briefly the key features of each of the components.

Patient Enrolment. The initial applications installed were patient enrolment, and disease case registration. The enrolment function captures the basic demographic information of the centre patients, by pre-enrolling them when referrals are received at a centre; these are completed online during an interview when the patient arrives. Some of the data collected include name, address, referring physician, sex, birth date, insurance information, person to contact, patient status and last contact date. The enrolment function provides a central patient index with access by name, chart number or insurance number. Attached to the Honeywell computers are Pitney-Bowes embosser plate makers. Authorized users can ask the system to create automatically an embosser plate or print a chart face-sheet for any enrolled patient.



Case Registration. The disease case registration module captures the fundamental items of data related to each known primary neoplasm for a patient. Some of these items of information include site of disease, histology code, data of diagnosis, date of first symptom, date of first treatment, residence at the time of diagnosis, method of confirmation and TNM staging. As part of this sub-system, extent of disease information

is recorded for the three sites: breast, larynx and cervix. The raw extent of disease information is entered into the system and the correct TNM and stage are coded automatically for these sites. Work is underway to automate the staging of more sites. The content of the extent of disease database and the rules for automatically coding TNM and stage were developed by an Extent of Disease Subcommittee.

Medical Services Reporting. A medical services reporting (MSR) subsystem records each service provided to patients by the regional cancer centre. The summary of the patients' visits, chemotherapy and radiotherapy treatments, and procedures performed are maintained in chronological sequence by date of service. The system also allows the recording of any non-neoplastic condition for which the patient is seen or treated.

Multiple Skin Lesions. Records on multiple skin lesions are maintained through the MSR system. Only one case registration is created on each skin lesion for each histology. Subsequent skin lesions are entered and maintained through this system.

Letter Follow-up. A letter follow-up system is available to produce letters to referring physicians for patients who are no longer seen at the centres. The letters are generated automatically based on the follow-up period on the patient's enrolment record.

Chart Tracking. A chart tracking system will monitor the movement of the medical chart throughout the centres. All charts now have bar code labels to enable chart numbers to be read by a light pen for ease in use of this facility.

Progress Notes. Progress notes are being automated through the IBM microcomputers in a local area network and through the use of word processing software. Notes will be entered through a microcomputer and letters to physicians following the case can easily be printed. The notes then will be transferred to the Honeywell system where the three most recent pages can be viewed from any terminal in the centre.

Referring Physicians. A referring physician's subsystem collects the names, addresses and OHIP information on doctors who refer patients to the centre. This file is an integral part of the enrolment, letter follow-up, and OHIP billing systems.

Scheduling. PCMS includes a patient appointment scheduling subsystem which provides up-to-date information instantly throughout the centre. Additions to the system will generate online appointment cards and, by copying schedules from one day to another, will make it easier to book appointments. An interface system will link medical services reporting, OHIP billing and scheduling to provide a means of ensuring the quality, reliability and completeness of the data. When patients arrive for their appointments, they will be checked into the system. Skeleton MSR and OHIP billing records will be written automatically. Periodically, reminder reports can be produced to identify skeleton records, which have not been completed.

Outreach. PCMS will play a major role in the establishment of outreach programs within the regional cancer centres. Through telephone links to the centres' computers, outreach facilities will have access to all of the PCMS software to assist in the management of patients.

Order Entry and Results Reporting. For the future, we plan, an order entry and results reporting feature, which will provide a mechanism for entering tests being ordered for patient and record the results when they are received. Eventually, each centre would like to interact with its host hospital so that test orders and results can be transferred electronically.

Research and Statistical Systems

To derive the full value of the data assembled in the Foundation's databases, tools are required for analysis. Data are available on more than 500,000 cancer patients over a period of 20 years. Such a volume of data requires computer programs to perform a wide variety of analyses such as cohort studies, trend analyses, incidence, mortality and survival rates calculations, production of indices of reliability, trends in referral patterns, and evaluation of changes in length of stay in hospitals.

Statistical Library. A library of statistical programs is being assembled from several sources. The Foundation has obtained commercial packages such as SAS, SPSS and BMDP and installed these on the IBM and Honeywell computers, and on the local microcomputer network at Head Office. Other data analysis programs were contributed by such institutions as Statistics Canada, Health and Welfare Canada, the Ontario Cancer Institute, and the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute. Finally, to enrich the library, Information Systems' staff is writing new analytical programs in consultation with the Division of Epidemiology and Statistics.



Research Data Entry. At present, data entry for special research projects is handled by an easy-to-use, flexible online system provided by CyCare Canada Ltd. This system can store 10,000 records with up to 512 characters of data in each. Several applications can have their own customized screens for entering and displaying data.

Quality Assurance. The quality of data in the Foundation's computer system is

assured in two basic ways: by preventing errors; and by detecting and correcting them. Preventable errors can occur during data collection, data entry or data processing. Data collection errors can be traced to poorly worded questions or ambiguous and incomplete answers. Data entry errors are edited by online and batch computer systems and data with errors are not accepted into the data base. Processing errors can be traced to rare hardware failures, or more frequently, to errors in programs. These can be prevented by careful program design and extensive testing before implementation. Errors caused by unauthorized users are prevented by passwords and other appropriate security features. Incorrect data are detected by batch programs run periodically to analyze all files. Several of the Foundation's systems have the facility for double entry of the same data.

The Division of Epidemiology and Statistics is in the process of establishing a quality-assurance program whereby data is re-abstracted and entered into a test data base. These new data are then compared with the original data and differences are analyzed to determine the origin of any discrepancies. The use of the information stored in the data base for research and patient care remains the ultimate test of the data quality.

Clinical Studies. We are in the process of defining the requirements for a clinical studies package. This system will assist in determining patients eligible for studies and will print reminders on the daily lists of scheduled appointments when tests, treatment and reports are required for the study. As designed, the new system can be used for either prospective or retrospective studies.

Potential Future Applications

In planning for future computer requirements, Information Systems is guided by the expressed needs of its users, and by the rapidly changing technological environment. The ideas described here represent potential applications which are not yet incorporated into the actual development plans for Information Systems.

Voice Input. The future of data entry is "hands-free" operation and the technology, although available, is only in a prototype form. However, within the next few years this will be a feasible and desirable means of data entry. In this system users will register themselves by repeating into a microphone words, numbers and letters presented on a terminal. The voice pattern of the individual is stored in the data base along with the item which is displayed on the screen. During data entry, that item is recorded whenever a known pattern is recognized.

Regnet. Through dial-up facilities, the Foundation could grant researchers and regional cancer centres, access to a data bank of incidence data for the province. Data would be presented based on a variety of options for example by year, by site, by county. No identifying information would be provided. Since any use of data may be subject to errors in interpretation because of inherent problems with data due to changes in reporting mechanisms — county boundary definitions or ICD coding — this data will not be made available until the Division of Epidemiology and Statistics has published its monograph on Cancer Incidence in Ontario. Such a monograph

would alert users to these points and provide appropriate footnotes in problem areas. In the future we hope to use computer-assisted instruction to provide state-of-the-art information on cancer treatment trials and other related topics. A dial-in feature would give referring physicians or hospitals access to the Foundation's information banks.

Pharmacy. The Foundation hopes to set up a means of monitoring the use of chemotherapeutic drugs. A complete history of a patient's drug history would be recorded, including reactions and allergies. As well, the system would monitor the cost of drugs administered.

Nursing. We hope to introduce a computerized nursing care planning module. The data collected and managed would relate to patient's responses to intervention, signs, symptoms, outcomes and other nursing-related factors. Such a system would assist the nurse practitioner in the management of the patient.

CO-ORDINATION AND MANAGEMENT OF INFORMATION SERVICES

While the provision of computing facilities is co-ordinated through the Information Systems Department located at the Foundation's Head Office on 7 Overlea Boulevard in Toronto, each regional cancer centre and the staff of the Division of Epidemiology and Statistics actively participate in the planning and implementation of these services. The Committee on Information Systems, chaired by Dr. R. D. T. Jenkin, provides guidance in terms of policies, facilities and priorities for service. A Computer Users' Group with representation from all centres reports to this committee. This group developed the original requirements for the PCMS. Recently it has become more active in liaising between Information Systems and the users in the regional cancer centres to solve on-going problems, to identify new requirements, and to keep users informed about plans for changes in computing applications and/or hardware. In many centres the member of the Computer Users' Group has set up a local users' group to ensure the return flow of information.

Each regional cancer centre also has a computer co-ordinator, who is responsible for the day-to-day running of the local system. They back-up the computer's data base and run the centre's daily reports. They also co-ordinate the repair of any malfunctioning hardware. To assist the co-ordinators in handling an increasingly complex computing system, Information Systems has implemented a "hotline" service through which all problems and queries are referred for prompt resolution.

Information Systems has also established a regular "INFOLETTER" to provide users with the latest news on Information Systems.

Without the interest and dedication of the responsible committees, the computer co-ordinators, the regional cancer centres' directors and the head of the Division of Epidemiology and Statistics and her staff, we could never have achieved the current high level of computerization. Even more important has been the patience and perseverance of the users in the centres and Head Office, who have coped so well when the computer was introduced into their working lives.

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APPENDICES



APPENDIX A

BEQUESTS AND OTHER DONATIONS

The Foundation was the grateful recipient of legacies, bequests and other donations totalling \$2,422,886 for the fiscal year ending March 31, 1984, which are of inestimable value to the Foundation's program.

Legacies of \$1,000 or over were received from the following estates:

The late Dorothy Elizabeth Baker, Orillia	\$ 8,000
— Dr. Russell G. Birrell, Toronto for research	30,000 (part)
— Ethel Mary Black, Toronto	30,532
— Grace Marion Brown, Ottawa for education and research	4,320 (part)
— Laura May Bunston, Thornbury	2,138
— Iva Minnie Cooke, London for use at London Centre	1,000
— Mabel Louise Curry, Toronto	2,500
— Alberta McNab Daly, Toronto	16,415 (part)
— Violet May Downey, Toronto	20,000 (part)
— John Archie Downie, Glencoe	1,000
— Eldred Durham, Toronto for research (Ann and Eldred Durham Trust Fund)	7,898 (part)
— Victorine Agnes Dwyer, Carleton Place	12,936
— Annie Elizabeth Fairhurst, Newmarket	5,696
— Annice Edith Forester, Toronto	9,500 (part)
— John Jacob Freedman, Toronto	119,000 (part)
— Clara May Hall, London for use at London Centre	1,000
— Harriet Landsborough Harkness, London for research at London Centre	9,583
— Bernard George Heaven, Hamilton	1,000
— Marion Lucille Hinde, Toronto for research in leukemia	6,000
— May Johnston, London for research at London Centre	1,611
— Annie Augusta Kates, Toronto	3,870 (part)

- Lorenz Koehler, London for research at London Centre	61,658 (part)
- Anna Elizabeth Korn, Toronto for research	10,000
- Mona Leighton, Toronto	45,911
- Maurice Martin Levac, Smiths Falls for use at: Kingston Centre	2,500
Quinte-Thousand Islands Lodge	2,500
- Mary Charron Emily Levac, Smiths Falls for use at: Kingston Centre	2,500
Quinte-Thousand Islands Lodge	2,500
- Reginald J. Lewis, Toronto	30,000 (part)
- Lena Marie Marsh, Newmarket	3,683 (part)
- Isobel Matheson, Goderich	13,950 (part)
- Margaret Ann McLennan Village of Glamis, County of Bruce	12,447
- Ellen May McVicar, London for research at London Centre	1,285 (part)
- Dorothea Nina Monck, Port Dover	118,576
- Bertie Moore, London	26,250
- Bertie Moore, London for use at London Centre	5,000
- Lorna May Muir, London for research at London Centre	17,575
- Elsie Mulholland, Toronto	1,000
- Clara Freda Nodwell, Toronto	15,507 (part)
- Hilda J. North, London for use at London Centre	12,000 (part)
- Beatrice Pilon, Gatineau, Quebec for use at Ottawa Centre	3,000
General Hospital Division	5,000
- Maurice Benson Pollard, Waubashene	8,000 (part)
- Henrietta Richardson, Toronto	
- Bertha M. Richter, London (Richter Endowment Fund Trust) in memory of Martha Ann Richter and George Richter, for use at London Centre	114,000 (part)
- Clara B. Sanderson, Brantford (John A. Sanderson and Family Trust)	9,170 (part)
- Mildred K. Schanbaker, Burlington for research	3,115 (part)
- Olga Schonfeld, Windsor	1,595 (part)
- Catherine Snow, London for research at London Centre	1,000

- Louis Szel, Toronto for research	1,195 (part)
- Gary Martin Vloet, Kemptville for use at Maurice Grimes Lodge Ottawa Centre	10,000
- Edward Clive Watson, Ottawa for use at Ottawa Centre Civic Hospital Division	3,075 (part)
- Godfrey Bryant Webb, Toronto	400,000 (part)
- John Whittle, London for use at London Centre	14,737 (part)
- Muriel Eva Whitworth, Lucan	2,535
- Madeleine Wilson, St. Mary's for use at London Centre	2,400 (part)
- William Witherspoon, Toronto	1,000
- William H. Woods, London for research at London Centre	187,470 (part)

Donations of \$1,000 or more were received from the following:

- Associated Clubs and Contractors' Hockey League, Toronto for annual visiting lectureship, (The Melatti Lectureship)	\$ 10,000
- Atomic Energy of Canada Limited, Kanata for use at Toronto-Bayview Centre	3,900
- Karl Bald, Toronto for use at Toronto-Bayview Centre	1,000
- Heather Burrell, Cambridge for Cambridge Outreach Program through Hamilton Centre	2,500
- Canadian Cancer Society, Toronto for use at Ottawa Centre	1,303
- L. Daubercies, Barry's Bay for use at Maurice Grimes Lodge Ottawa Centre	1,500
- James Dennett, Corunna for research at London Centre	1,000
- Cornelia Fuykschot, Gananoque for special services to needy cancer patients	1,000
- Dr. David Ginsburg, Kingston for visiting lecturers, Kingston Centre	1,000
- Leaside High School, Toronto for use at Toronto-Bayview Centre	3,048

- Lorraine Chapter, I.O.D.E., Ottawa for use at Ottawa Centre	1,200
- Mary MacLennan, Windsor for research	1,000
- Mr. and Mrs. F. Maier, Thunder Bay for use at Thunder Bay Centre	5,000
- T. Donald Miller Foundation, Toronto for use at Princess Margaret Hospital	2,000
- N. R. Murphy Foundation, Cambridge for Cambridge Outreach Program through Hamilton Centre	12,000
- Ottawa Civic Hospital Foundation for use at Ottawa Centre	1,243
- Rebekah Assembly of Ontario, Belleville for research at London Centre	4,287
- Colonel Harland Sanders Charitable Organization, Weston for research at London Centre	1,060
- Skyline Manufacturing Ltd., Downsview for research at Toronto-Bayview Centre	3,000
- Toronto General Hospital for research at Ottawa Centre	2,000
- The Toronto Star, Toronto	1,000
- University of New Brunswick, Fredericton	3,000
- University of Ottawa, Ottawa for research at Ottawa Centre	2,810
- War Memorial Children's Hospital, London for research at London Centre	4,109
- West Ottawa Lions Club, Ottawa for use at Ottawa Centre	2,000
- Mr. and Mrs. G. D. White, Kingston for special services to needy cancer patients	1,000
- W. G. M. Wilson, London for the Harold E. Johns Summer Studentships in Medical Physics Program	1,432
- H. Wrigglesworth, Don Mills (Dorothy Wrigglesworth Cancer Research Fund)	1,000

The Foundation is grateful to these donors and to the many others not listed above and reveres the memory of those who extended their lifetime efforts to fight cancer when making their wills. These welcome additions to our research and other funds ensure that the Foundation's extensive research program can proceed at a time of financial constraints and inflated costs.

APPENDIX B

LIST OF ARTICLES PUBLISHED 1983

RESEARCH ASSOCIATES AND GRANTEES, AND MEMBERS OF
THE STAFFS OF THE ONTARIO CANCER TREATMENT
AND RESEARCH FOUNDATION AND THE
REGIONAL CANCER CENTRES

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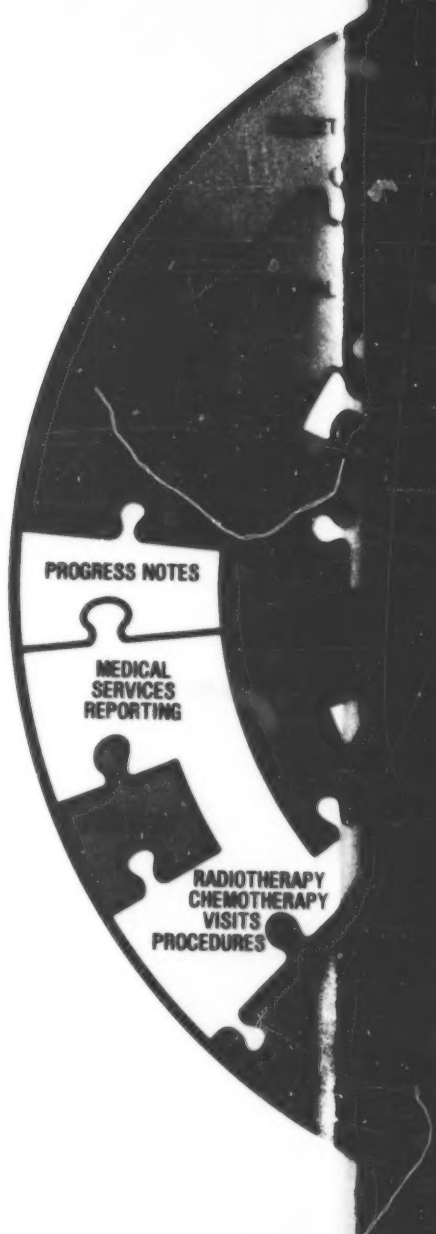
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